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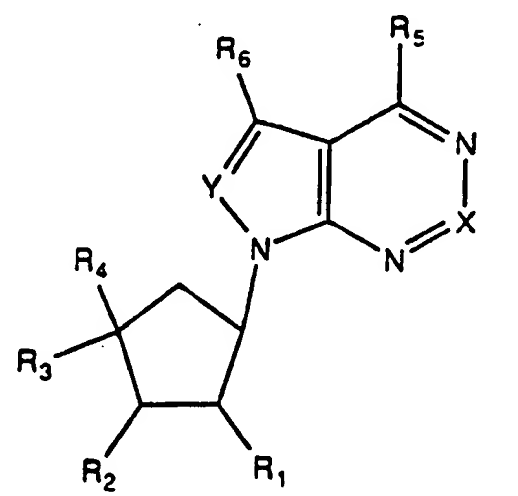
(54) Title: HETEROCYCLIC SUBSTITUTED CYCLOPENTANE COMPOUNDS

(57) Abstract



(I)

The present invention provides new heterocyclic substituted cyclopentane compounds of formula (I), wherein X is -N or -CR$_7$, where R$_7$ is hydrogen, halogen, loweralkyl, loweralkoxy or -S-loweralkyl; Y is -N or -CH; R$_1$ and R$_2$ are each independently hydrogen, hydroxy, alkoxy, or acyloxy or R$_1$ and R$_2$ are both hydroxy protected with an individual hydroxy protecting group or with a single dihydroxy-protecting group or R$_1$ and R$_2$ are absent and there is a double bond between the carbon atoms to which R$_1$ and R$_2$ are attached; R$_3$ is hydrogen, hydroxy, loweralkyl or alkoxy; R$_4$ is (a) hydrogen, (b) amino, (c) halogen, (d) hydroxy, (e) sulfonamido, (f) -P(O)(OH)$_2$, (g) -P(O)-R$_8$R$_9$, wherein R$_8$ and R$_9$ are each independently hydrogen, hydroxy, loweralkyl, aryl or arylalkyl, (h) -NHR$_{10}$, wherein R$_{10}$ is hydrogen or an amino protecting group, (i) -NHC(O)NHR$_{11}$, where R$_{11}$ is hydrogen or loweralkyl, or (j) -A-R$_{12}$ wherein A is O, S(O)$_n$ or -N(R$_{13}$)- wherein R$_{13}$ is hydrogen or loweralkyl, n is zero, one or two, and R$_{12}$ is hydrogen, loweralkyl, alkylsulfonyl, acyl, alkoxycarbonyl, aryl, heteroaryl, arylalkyl, arylsulfonyl, haloalkyl, heteroarylalkyl, heteroarylsulfonyl, aminoalkyl or heterocyclic or (k) R$_4$ is a ring N-member of a heteroaryl or heterocycle; or R$_3$ and R$_4$ taken together are =O, or taken together with the carbon atom to which they are attached, form a spirocyclic ring; R$_5$ is hydrogen, loweralkyl, aryl, arylalkyl, heteroaryl, amino, alkylamino, alkoxy, acylamino, arylalkynyl, arylamino, arylmercapto, alkylmercapto, halogen, heterocyclic, hydrazino, -NHC(O)NH$_2$, or -NR$_{14}$R$_{15}$ wherein R$_{14}$ and R$_{15}$ are each independently hydrogen or an amino protecting group or -NR$_{14}$R$_{15}$ is a nitrogen containing heterocycle of 5 to 7 members; and R$_6$ is loweralkyl, cycloalkyl, alkenyl, alkynyl, alkoxy, alkoxycarbonyl, carboxy, aryl, heteroaryl, heteroarylalkyl, arylalkyl, arylalkenyl, arylalkynyl, cyano, halogen, heteroarylalkynyl, or -C(O)NHR$_{16}$, wherein R$_{16}$ is alkyl, aryl, or heterocyclic. The present invention also provides pharmaceutical compositions containing such compounds and methods of using such compounds for inhibiting adenosine kinase.

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HETEROCYCLIC SUBSTITUTED CYCLOPENTANE COMPOUNDS

CROSS REFERENCE TO RELATED APPLICATIONS

This application is a continuation-in-part of U. S. Serial No. 08/472,486, filed June 7, 1995, which is related to the following applications which are incorporated herein by reference: U. S. Serial No. 08/473,091, filed, June 7, 1995, and U. S. Serial No. 08/472,806, filed, June 7, 1995.

TECHNICAL FIELD

The present invention relates to new heterocyclic substituted cyclopentane compounds, which are useful in inhibiting adenosine kinase, to pharmaceutical compositions containing such compounds and to a method of using such compounds for inhibiting adenosine kinase.

BACKGROUND OF THE INVENTION

Adenosine kinase (ATP:adenosine 5'-phosphotransferase, EC 2.7.1.20) is a ubiquitous enzyme which catalyzes the phosphorylation of adenosine to AMP, using ATP, preferentially, as the phosphate source. Magnesium is also required for the reaction, and the true cosubstrate is probably the $MgATP^{2-}$ complex (Palella, *et al.*, *J. Biol. Chem.* 1980, **255**: 5264-5269). Adenosine kinase has broad tissue and species distribution, and has been isolated from yeast (Leibach, *et al.*, *Hoppe-Seyler's Z. Physiol. Chem.* 1971, **352**: 328-344), a variety of mammalian sources (*e.g.* Miller, *et al.*, *J. Biol. Chem.* 1979, **254**: 2339-2345; Palella, *et al.*, *J. Biol. Chem.* 1980, **255**: 5264-5269; Yamada, *et al.*, *Comp. Biochem. Physiol.* 1982, **71B**: 367-372; Rottlan and Miras-Portugal, *Eur. J. Biochem.*, 1985, **151**: 365-371) and certain microorganisms (*e.g.* Lobelle-Rich and Reeves, *Am. J. Trop. Med. Hyg.* 1983, **32**: 976-979; Datta, *et al.*, *J. Biol. Chem.* 1987, **262**: 5515-5521). It has been found to be present in virtually every human tissue assayed including kidney, liver, brain, spleen, placenta and pancreas (Andres and Fox, *J. Biol. Chem.* 1979, **254**: 11388-11393).

Adenosine kinase is a key enzyme in the control of the cellular concentrations of adenosine (Arch and Newsholme, *Essays Biochem.* 1978, **14**: 82-123). Adenosine is a purine nucleoside that is an intermediate in the pathways of purine nucleotide degradation and salvage. In addition, adenosine has many important physiologic effects, many of which are mediated through the activation of specific ectocellular receptors, termed P_1

receptors (Burnstock, in *Cell Membrane Receptors for Drugs and Hormones,* 1978, (Bolis and Straub, eds) Raven, New York, pp. 107-118; Fredholm, *et al., Pharmacol. Rev.* 1994, **46**: 143-156). In the central nervous system, adenosine inhibits the release of certain neurotransmitters (Corradetti, *et al., Eur. J. Pharmacol.* 1984, **104**: 19-26), stabilizes membrane potential (Rudolphi, *et al., Cerebrovasc. Brain Metab. Rev.* 1992, **4**: 346-360), functions as an endogenous anticonvulsant (Dragunow, *Trends Pharmacol. Sci.* 1986, **7**: 128-130) and may have a role as an endogenous neuroprotective agent (Rudolphi, *et al., Trends Pharmacol. Sci.* 1992, **13**: 439-445). Adenosine has also been implicated in modulating transmission in pain pathways in the spinal cord (Sawynok, *et al., Br. J. Pharmacol.* 1986, **88**: 923-930), and in mediating the analgesic effects of morphine (Sweeney, *et al., J. Pharmacol. Exp. Ther.* 1987, **243**: 657-665). In the immune system, adenosine inhibits certain neutrophil functions and exhibits anti-inflammatory effects (Cronstein, *J. Appl. Physiol.* 1994, **76**: 5-13). Adenosine also exerts a variety of effects on the cardiovascular system, including vasodilation, impairment of atrioventricular conduction and endogenous cardioprotection in myocardial ischemia and reperfusion (Mullane and Williams, in *Adenosine and Adenosine Receptors,* 1990 (Williams, ed) Humana Press, New Jersey, pp. 289-334). The widespread actions of adenosine also include effects on the renal, respiratory, gastrointestinal and reproductive systems, as well as on blood cells and adipocytes.

Endogenous adenosine release appears to have a role as a natural defense mechanism in various pathophysiologic conditions, including cerebral and myocardial ischemia, seizures, pain, inflammation and sepsis. While adenosine is normally present at low levels in the extracellular space, its release is locally enhanced at the site(s) of excessive cellular activity, trauma or metabolic stress. Once in the extracellular space, adenosine activates specific extracellular receptors to elicit a variety of responses which tend to restore cellular function towards normal (Bruns, *Nucleosides Nucleotides*, 1991, **10**: 931-943; Miller and Hsu, *J. Neurotrauma*, 1992, **9**: S563-S577). Adenosine has a half-life measured in seconds in extracellular fluids (Moser, *et al., Am. J. Physiol.* 1989, **25**: C799-C806), and its endogenous actions are therefore highly localized.

The inhibition of adenosine kinase can result in augmentation of the local adenosine concentrations at foci of tissue injury, further enhancing

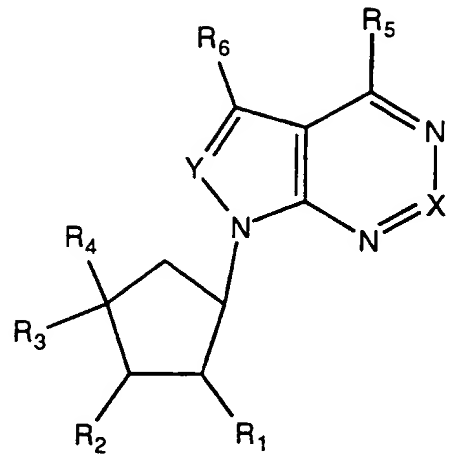
cytoprotection. This effect is likely to be most pronounced at tissue sites where trauma results in increased adenosine production, thereby minimizing systemic toxicities. Pharmacologic compounds directed towards adenosine kinase inhibition provide potentially effective new therapies for disorders benefited by the site- and event-specific potentiation of adenosine.

A number of compounds have been reported to inhibit adenosine kinase. The most potent of these include 5'-amino,5'-deoxyadenosine (Miller, *et al., J. Biol. Chem.* 1979, **254**: 2339-2345), 5-iodotubercidin (Wotring and Townsend, *Cancer Res.* 1979, **39**: 3018-3023) and 5'-deoxy-5-iodotubercidin (Davies, *et al., Biochem. Pharmacol.* 1984, **33**: 347-355).

Adenosine kinase is also responsible for the activation of many pharmacologically active nucleosides (Miller, *et al., J. Biol. Chem.* 1979, **254**: 2339-2345), including tubercidin, formycin, ribavirin, pyrazofurin and 6-(methylmercapto)purine riboside. These purine nucleoside analogs represent an important group of antimetabolites which possess cytotoxic, anticancer and antiviral properties. They serve as substrates for adenosine kinase and are phosphorylated by the enzyme to generate the active form. The loss of adenosine kinase activity has been implicated as a mechanism of cellular resistance to the pharmacological effects of these nucleoside analogs (*e.g.* Bennett, *et al., Mol. Pharmacol.*, 1966, **2**: 432-443; Caldwell, *et al., Can. J. Biochem.*, 1967, **45**: 735-744; Suttle, *et al., Europ. J. Cancer*, 1981, **17**: 43-51). Decreased cellular levels of adenosine kinase have also been associated with resistance to the toxic effects of 2'-deoxyadenosine (Hershfield and Kredich, *Proc. Natl. Acad. Sci. USA*, 1980, **77**: 4292-4296). The accumulation of deoxyadenosine triphosphate (dATP), derived from the phosphorylation of 2'-deoxyadenosine, has been suggested as a toxic mechanism in the immune defect associated with inheritable adenosine deaminase deficiency (Kredich and Hershfield, in *The Metabolic Basis of Inherited Diseases*, 1989 (Scriver, *et al.*, eds), McGarw-Hill, New York, pp. 1045-1075).

BRIEF SUMMARY OF THE INVENTION

In one aspect, the present invention provides a heterocyclic substituted cyclopentane compound that acts as an adenosine kinase inhibitor. A compound of the present invention is a compound of the Formula I, below:



Formula I

wherein

X is -N or -CR_7 where R_7 is hydrogen, halogen, loweralkyl, loweralkoxy or -S-loweralkyl;

Y is -N or -CH;

R_1 and R_2 are each independently hydrogen, hydroxy, alkoxy, or acyloxy or R_1 and R_2 are both hydroxy protected with an individual hydroxy protecting group or with a single dihydroxy-protecting group or R_1 and R_2 are absent and there is a double bond between the carbon atoms to which R_1 and R_2 are attached;

R_3 is hydrogen, hydroxy, loweralkyl or alkoxy;

R_4 is a) hydrogen, b) amino, c) halogen, d) hydroxy, e) sufonamido, f) -P(O)$(OH)_2$, g) -P(O)-R_8R_9 wherein R_8 and R_9 are each independently hydrogen, hydroxy, loweralkyl, aryl, or arylalkyl, h) -NHR_{10} wherein R_{10} is hydrogen or an amino protecting group, i) -NHC(O)NHR_{11} where R_{11} is hydrogen or loweralkyl, j) -AR_{12} wherein A is O, $S(O)_n$ or -$N(R_{13})$- wherein R_{13} is hydrogen or loweralkyl, n is zero, one or two, and R_{12} is hydrogen, loweralkyl, alkylsulfonyl, acyl, alkoxycarbonyl, aryl, arylalkyl, heteroaryl, arylsulfonyl, haloalkyl, heteroarylalkyl, heteroarylsulfonyl, aminoalkyl or heterocyclic, or k) R_4 is a nitrogen atom of a heteroaryl or heterocyclic ring; or

R_3 and R_4 taken together are =O, or taken together with the carbon atom to which they are attached form a spirocyclic ring;

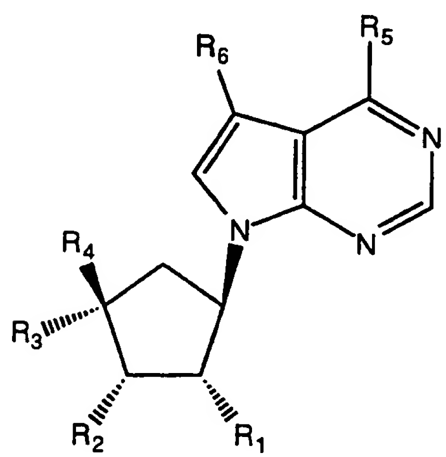
R_5 is hydrogen, loweralkyl, aryl, arylalkyl, heteroaryl, amino, alkylamino, alkoxy, acylamino, arylalkenyl, arylalkynyl, arylamino, arylmercapto, halogen, heterocyclic, hydrazino, thioalkoxy, -NHC(O)NH_2, or

$-NR_{14}R_{15}$ wherein R_{14} and R_{15} are each independently hydrogen or an amino protecting group or $-NR_{14}R_{15}$ is a nitrogen containing heterocycle of 5 to 7 members; and

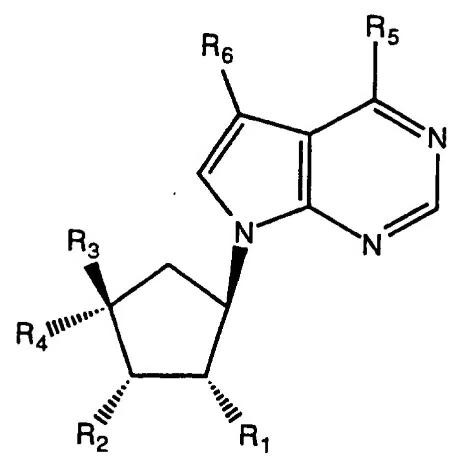
R_6 is loweralkyl, cycloalkyl, alkenyl, alkynyl, alkoxy, alkoxycarbonyl, carboxy, aryl, heteroaryl, heteroarylalkyl, arylalkyl, arylalkenyl, arylalkynyl, heterocyclicalkyl, heterocyclicalkenyl, heterocyclicalkynyl, cyano, halogen, heteroarylalkynyl, or $-C(O)NHR_{16}$ wherein R_{16} is alkyl, aryl, or heterocyclic.

In a preferred embodiment, X and Y are both -CH, R_1 and R_2 are -OH; R_3 is hydrogen: R_4 is amino, hydroxyl, $-NHR_{10}$ or $-NR_{12}R_{13}$ where R_{10}, R_{12} and R_{13} are as defined in claim 1, R_5 is amino, arylalkyl, arylalkynyl, arylamino or halogen and R_6 is aryl, arylalkyl, arylalkenyl, arylalkynyl, or halogen. More preferably, R_4 is amino, methylamino, dimethylamino, carbamate, acylamino or heteroarylacylamino; R_5 is chloro, amino, phenylamino or 2-phenylethynyl; and R_6 is chloro, iodo, phenyl, 2-phenylethyl or 2-phenylethynyl.

In a more preferred embodiment, a compound of the present invention is a compound of Formula II, or IV below:



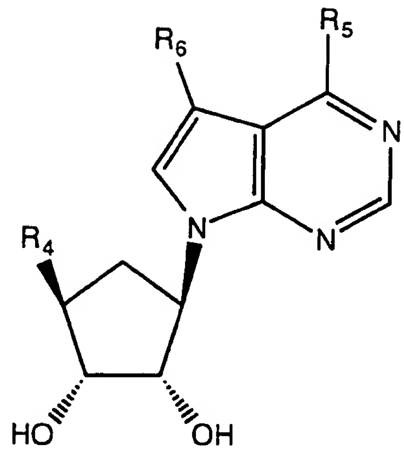
Formula II



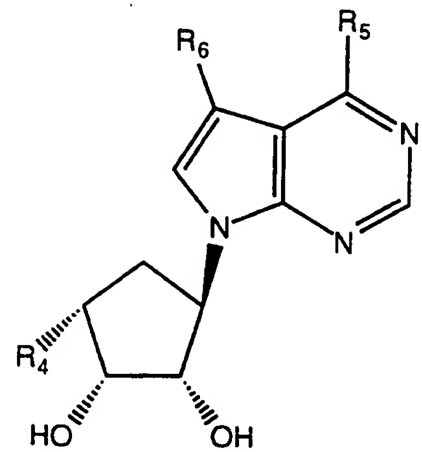
Formula IV

where R_1, R_2, R_3, R_4, R_5 and R_6 are as defined above.

An especially preferred compound of the present invention has the Formula III or V below:



Formula III



Formula V

where R_4, R_5 and R_6 are as defined above. Preferred values of R_4, R_5 and R_6 are the same as set forth above. Exemplary and preferred compounds having the Formula I, II, or III are:

N7-((1'R,2'S,3'R,4'S)-2',3',4'-trihydroxycyclopentyl)-4,5-dichloro-pyrrolopyrimidine,

N7-((1'R,2'S,3'R,4'S)-2',3',4'-trihydroxycyclopentyl)-4-chloro-5-iodo-pyrrolopyrimidine,

N7-((1'R,2'S,3'R,4'S)-2',3',4'-trihydroxycyclopentyl)-4-amino-5-iodo-pyrrolopyrimidine,

N7-((1'R,2'S,3'R,4'S)-2',3',4'-trihydroxycyclopentyl)-4-(phenyl)amino-5-iodo-pyrrolopyrimidine,

N7-((1'R,2'S,3'R,4'S)-2',3',4' trihydroxycyclopentyl)-4-chloro-5-phenyl-pyrrolopyrimidine,

N7-((1'R,2'S,3'R,4'S)-2',3',4'-trihydroxycyclopentyl)-4-amino-5-phenyl-pyrrolopyrimidine,

N7-((1'R,2'S,3'R,4'S)-2',3',4'-trihydroxycyclopentyl)-4-(phenyl)amino-5-phenyl-pyrrolopyrimidine,

N7-((1'R,2'S,3'R,4'S)-2',3',4'-trihydroxycyclopentyl)-4,5-bis-phenylacetylenyl-pyrrolopyrimidine,

N7-((1'R,2'S,3'R,4'S)-2',3',4'-trihydroxycyclopentyl)-4-chloro-5-phenylacetylenyl-pyrrolopyrimidine,

N7-((1'R,2'S,3'R,4'S)-2',3',4'-trihydroxycyclopentyl)-4-amino-5-phenylacetylenyl-pyrrolopyrimidine,

N7-((1'R,2'S,3'R,4'S)-2',3',4'-trihydroxycyclopentyl)-4-amino-5-((2-phenyl)ethyl)-pyrrolopyrimidine,

N7-((1'R,2'S,3'R,4'S)-2',3'-dihydroxy-4'-amino-cyclopentyl)-4-chloro-5-iodo-pyrrolopyrimidine,

N7-((1'R,2'S,3'R,4'S)-2',3'-dihydroxy-4'-amino-cyclopentyl)-4-amino-5-iodo-pyrrolopyrimidine,

N7-((1'R,2'S,3'R,4'S)-2',3'-dihydroxy-4'-(bis-t-butoxycarbonylamino)-cyclopentyl)-4-chloro-5-iodo pyrrolopyrimidine,

N7-((1'R,2'S,3'R,4'S)-2',3'-dihydroxy-4'-(t-butoxycarbonylamino)-cyclopentyl)-4-amino-5-iodo-pyrrolopyrimidine,

N7-((1'R,2'S,3'R,4'S)-2',3'-dihydroxy-4'-(methyl)amino-cyclopentyl)-4-chloro-5-methyl-pyrrolopyrimidine,

N7-((1'R,2'S,3'R,4'S)-2',3'-dihydroxy-4'-(dimethyl)amino-cyclopentyl)-4-chloro-5-iodo-pyrrolopyrimidine and

N7-((1'R,4'S)-cis-4'-amino-2'-cyclopentenyl)-4-chloro-5-iodo-pyrrolopyrimidine,

N7-((1'R,2'S,3'R,4'S)-2',3'-dihydroxy-4'-(3"-nicotinoyl)amino-cyclopentyl)-4-chloro-5-iodo-pyrrolopyrimidine,

N7-((1'R,2'S,3'R,4'S)-2',3'-dihydroxy-4'-(3"-chloro-pyridazin-6"-yl)amino-cyclopentyl)-4-amino-5-iodo-pyrrolo-pyrimidine,

N7-((1'R,2'S,3'R,4'S)-2',3'-dihydroxy-4'-(2"-pyrimidinyl)-amino-cyclopentyl)-4-amino-5-iodo-pyrrolopyrimidine,

N7-((1'R,2'S,3'R,4'S)-2',3'-dihydroxy-4'-(2"-pyridinylacetyl)amino-cyclopentyl)-4-chloro-5-iodo-pyrrolopyrimidine,

N7-((1'R,2'S,3'R,4'S)-2',3'-dihydroxy-4'-(dimethylaminoacetyl)amino-cyclopentyl)-4-chloro-5-iodo-pyrrolo-pyrimidine,

N7-((1'R,2'S,3'R,4'S)-2',3'-dihydroxy-4'-(3"-pyridinylacetyl)amino-cyclopentyl)-4-chloro-5-iodo-pyrrolopyrimidine,

N7-((1'R,2'S,3'R,4'S)-2',3'-dihydroxy-4'-(N-t-butoxycarbonylamino-acetyl)amino-cyclopentyl)-4-chloro-5-iodo-pyrrolo-pyrimidine,

N7-((1'R,2'S,3'R,4'S)-2',3'-dihydroxy-4'-(amino-acetyl)amino-cyclopentyl)-4-chloro-5-iodo-pyrrolopyrimidine,

N7-((1'R,2'S,3'R,4'S)-2',3'-dihydroxy-4'-(4"-bromo phenyl)aminocyclopentyl)-4-chloro-5-iodo-pyrrolopyrimidine,

N7-((1'R,4'R)-cis-4'-amino-cyclopentyl)-4-chloro-5-iodo-pyrrolopyrimidine,

N7-((1'R,2'S,3'R,4'S)-2',3'-dihydroxy-4'-(bis-t-butoxycarbonylamino)-cyclopentyl)-4-chloro-5-phenyl-pyrrolopyrimidine,

N7-((1'R,2'S,3'R,4'S)-2',3'-dihydroxy-4'-amino-cyclopentyl)-4-chloro-5-phenyl-pyrrolopyrimidine,

N7-((1'R,2'S,3'R,4'S)-2',3'-dihydroxy-4'-(t-butoxycarbonyl-methylene)-amino-cyclopentyl)-4-chloro-5-iodo-pyrrolo-pyrimidine,

N7-((1'R,2'S,3'R,4'S)-2',3'-dihydroxy-4'-(carboxy-methylene)amino-cyclopentyl)-4-chloro-5-iodo-pyrrolopyrimidine,

N7-((1'R,4'S)-4'-((N-(2",4"-dinitrophenyl-sulfonyl)-(O-t-butyl)-L-asparaginyl)cyclopentenyl)-4-chloro-5-iodo-pyrrolo-pyrimidine,

N7-((1'R,2'S,3'R,4'S)-2',3'-dihydroxy-4'-(N-(2",4"-dinitrophenyl-sulfonyl)-O-t-butyl-L-asparaginyl)cyclopentyl)-4-chloro-5-iodo-pyrrolo-pyrimidine,

N7-((1'R,2'S,3'R,4'S)-2',3'-dihydroxy-4'-(N-(O-t-butyl)-L-asparaginyl)-cyclopentyl)-4-chloro-5-iodo-pyrrolopyrimidine,

N7-((1'R,2'S,3'R,4'S)-2',3'-dihydroxy-4'-(N-asparaginyl) amino-cyclopentyl)-4-chloro-5-iodo-pyrrolopyrimidine, and salts, amides or esters of the above-compounds. The meaning of salt, ester and amide is defined hereinafter.

In another aspect, the present invention provides a pharmaceutical composition comprising a compound of the present invention in combination with a pharmaceutically acceptable carrier. Preferred compounds are those set forth above that have the Formula I, II, III, IV or V. A compound is present in a therapeutically effective amount.

In another aspect, the present invention provides a method of inhibiting adenosine kinase comprising exposing an adenosine kinase to an effective inhibiting amount of a compound of the present invention. Where the adenosine kinase is located *in vivo*,.the compound is administered to the organism. Preferred compounds are the same as set forth above.

In another aspect, the present invention provides a method of treating cerebral ischemia, epilepsy, nociperception, inflammation and sepsis in a patient in need of such treatment, comprising administering to the patient a therapeutically effective amount of a compound of the present invention.

DETAILED DESCRIPTION OF THE INVENTION

I. The Invention

The present invention relates to new heterocyclic substituted cyclopentane compounds which are useful in inhibiting adenosine kinase, to pharmaceutical compositions containing such compounds and to a method of using such compounds for inhibiting adenosine kinase.

II. Compounds

The compounds of the invention comprise asymmetrically substituted carbon atoms. As a result, all stereoisomers of the compounds of the invention are meant to be included in the invention, including racemic mixtures, mixtures of diastereomers, as well as single diastereomers of the compounds of the invention. The terms "S" and "R" configuration, as used herein, are as defined by the IUPAC 1974 Recommendations for Section E, Fundamental Stereochemistry, Pure Appl. Chem. (1976) 45, 13-30.

In one aspect, the present invention provides heterocyclic substitute cyclopentane compounds that are adenosine kinase inhibitors. An adenosine kinase inhibitor of the present invention is a compound of the Formula I, shown above.

In a more preferred embodiment, an adenosine kinase inhibitor of the present invention is a compound of Formula II or IV, shown above.

Exemplary hydroxy protecting groups are acetyl and methylethylidene.

Exemplary R_4 groups are acetoxy, acetylamino, t-butoxycarbonylamino, methoxycarbonylamino, nicotinoylamino, dimethylamino, trifluoroacetylamino, phthalimido, chloro- and dimethyl-amino,-pyridazinyl, pyridinylamino, pyridinyloxy, methylimidazole-sulfonylamino, acetylmercapto, picolylmercapto, pyridinylmercapto, methyl- and aminoethyl-mercapto, diphenylphosphinyl, nicotinamide and imidazolyl.

Exemplary R_5 groups are halogen, amino, phenylamino, phenylacetylenyl, methoxy, and phenylmercapto.

Exemplary R_6 groups are halogen, phenyl, 2-phenylethyl, methyl, phenylacetylenyl, pyridinyl, carbomethoxy, carboxy, cyano, and cyclobutylcarboxamido.

Preferred compounds of the invention are compounds of Formula I, II or IV wherein X is -CH.

Other preferred compounds of the invention are compounds of Formula I, II or IV wherein R_1 and R_2 are -OH.

Other preferred compounds of the invention are compounds of Formula I, II or IV wherein R_4 is amino, hydroxyl, $-NHR_{10}$ or $-NR_{12}R_{13}$ where R_{10}, R_{12}, and R_{13} are as defined above.

Other preferred compounds of the invention are compounds of Formula I, II or IV wherein R_5 is amino, arylalkyl, arylalkynyl, arylamino or halo.

Other preferred compounds of the invention are compounds of Formula I, II or IV wherein R_6 is aryl, arylalkyl, arylalkenyl, arylalkynyl, and halogen.

Other preferred compounds of the invention are compounds of Formula I, II or IV wherein X is -CH; R_1 and R_2 are -OH; R_4 is amino, hydroxyl, $-NHR_{10}$ or $-NR_{12}R_{13}$ where R_{10}, R_{12} and R_{13} are as defined above, R_5 is amino, arylalkyl, arylalkynyl, arylamino or halogen and R_6 is aryl, arylalkyl, arylalkenyl, arylalkynyl, or halogen.

Other preferred compounds of the invention are compounds of Formula I, II or IV wherein R_3 is hydrogen and R_4 is hydroxy, amino, or $-NHR_{10}$ wherein R_{10} is hydrogen or an amino protecting group.

Other preferred compounds of the invention are compounds of Formula I, II or IV wherein R_4 is amino, methylamino, dimethylamino, carbamate, acylamino or heteroarylacylamino, R_5 is chloro, amino, phenylamino or 2-phenylethynyl; and R_6 is chloro, iodo, phenyl, 2-phenylethynyl or 2-phenylethyl.

More preferred compounds of the invention are compounds of Formula I, II or IV wherein X is CH; R_1 and R_2 are OH; R_3 is hydrogen; R_4 is amino, methylamino, dimethylamino, carbamate, acylamino or heteroarylacylamino; R_5 is chloro, amino, phenylamino or 2-phenylethynyl; and R_6 is chloro, iodo, phenyl, 2-phenylethyl or 2-phenylethynyl.

An especially preferred compound of the present invention has the Formula III or V, shown above.

Exemplary and preferred compounds having the Formula III or V are those wherein R_4 is hydroxyl and the values of R_5 and R_6 are: a) R_5 is Cl and R_6 is Cl, I, phenyl, or 2-phenylethynyl; b) R_5 is NH_2 and R_6 is I, phenyl, 2-phenylethyl or 2-phenylethynyl; c) R_5 is phenylamino and R_6 is I or phenyl; or d) R_5 is 2-phenylethynyl and R_6 is 2-phenylethynyl. Other exemplary and

preferred compounds having the Formula III are those wherein a) R_4 is NH_2, R_5 is Cl or NH_2 and R_6 is I; b) R_4 is Boc_2N, R_5 is Cl and R_6 is I; c) R_4 is NHBoc, R_5 is NH_2 and R_6 is I; d) R_4 is CH_3NH, R_5 is Cl and R_6 is CH_3; e) R_4 is $(CH_3)_2N$, R_5 is Cl and R_6 is I; f) R_4 is nicotinamide, R_5 is Cl and R_6 is I; g) R_4 is (3''-chloro-pyridazin-6''-yl)amino, R_5 is NH2, and R_6 is I; h) R4 is (2''-pyrimidinyl)amino, R_5 is NH2, and R_6 is I; i) R_4 is (3''-pyridinylacetyl)amino, R_5 is Cl and R_6 is I; j) R_4 is (N-t-butoxycarbonylaminoacetyl)amino, R_5 is Cl, and R_6 is I; k) R_4 is (aminoacetyl)amino, R_5 is Cl, and R_6 is I; l) R_4 is (dimethylaminoacetyl)amino, R_5 is Cl and R_6 is I; m) R_4 is (4''-bromophenyl)amino, R_5 is Cl and R_6 is I; n) R_4 is (pyridine-3''-yl)oxy, R_5 is Cl, and R_6 is I; o) R_4 is bis-(t-butoxycarbonyl-methylene)amino, R_5 is Cl and R_6 is I; p) R_4 is (carboxy-methylene)amino, R_5 is Cl, and R_6 is I; and q) R_4 is N-(2'',4''-dinitrophenylsulfonyl)-(O-t-butyl)-L-asparaginyl, R_5 is Cl and R_6 is I.

The present invention also contemplates salts, amides and esters of compounds having Formula I to V.

The term "acyl" as used herein refers to R_{17}CO-where R_{17} is loweralkyl, heteroaryl or heterocyclic.

The term "acyloxy" as used herein refers to R_{18}COO-where R_{18} is loweralkyl, heteroaryl or heterocyclic.

The term "alkanoylaminoalkyl" as used herein refers to -NHC(O)R_{19} wherein R_{19} is loweralkyl.

The term "alkanoyloxyalkyl" as used herein refers to -OC(O)R_{20} wherein R_{20} is loweralkyl.

The term "alkenyl" as used herein refers to branched or straight chain alkyl groups comprising 2 to 10 carbon atoms that has one or more carbon-carbon double bonds, including vinyl, propenyl, butenyl and the like.

The term "alkoxy" as used herein refers to R_{21}O where R_{21} is a loweralkyl or benzyl group. Representative alkoxy groups include methoxy, ethoxy, t-butoxy, benzyloxy and the like.

The term "alkoxycarbonyl" as used herein refers -C(O)OR_{22} wherein R_{22} is loweralkyl or cycloalkyl.

The term "alkoxycarbonyloxyalkyl" as used herein refers to -OC(O)OR_{23} wherein R_{23} is loweralkyl or cycloalkyl.

The term "alkoxycarbonylaminoalkyl" as used herein refers to -NHC(O)OR_{24} wherein R_{24} is loweralkyl.

The term "alkylamino" as used herein refers to NHR_{25} where R_{25} is a loweralkyl group.

The term "alkylmercapto" as used herein refers to SHR_{26} where R_{26} is a loweralkyl group.

The term "alkylsulfonyl" as used herein refers to SO_2R_{27} where R_{27} is a loweralkyl group.

The term "alkylaminocarbonylaminoalkyl" as used herein refers to -NHC(O)NHR$_{28}$ wherein R_{28} is loweralkyl.

The term "alkynyl" as used herein refers to branched or straight chain alkyl groups comprising 2 to 10 carbon atoms that has one or more carbon-carbon triple bonds, including ethynyl, propynyl, butynyl and the like.

The term "aroyloxyalkyl" as used herein refers to a loweralkyl radical -OC(O)R$_{29}$ wherein R_{29} is loweralkyl.

The term "aryl" as used herein refers to a phenyl or a C_9 or C_{10} bicyclic carbocyclic ring system having one or more aromatic rings, including naphthyl, tetrahydronaphthyl, indanyl, indenyl and the like. The term "aryl" includes aryl groups that are unsubstitued or substituted with one or more substituents independently selected from loweralkyl, alkoxy, halo-substituted loweralkyl, cyano, thioalkoxy, alkoxycaronyl, hydroxy, halo, mercapto, nitro, amino, alkylamino, dialkylamino, carboxaldehyde, carboxy and carboxamide.

The terms "arylalkyl, arylalkenyl and arylalkynyl" as used herein refer to an aryl group appended to an alkyl, alkenyl or alkynyl group, respectively

The term "arylamino" as used herein refers to an aryl group appended to an amino group.

The term "arylmercapto" as used herein refers to an aryl group appended to a mercapto (SH) group.

The term "dialkylamino" as used herein refers to -NR$_{30}$R$_{31}$ wherein R_{30} and R_{31} are independently selected from loweralkyl.

The term "halogen" or "halo" as used herein refers to Cl, Br, I and F.

The term "heteroaryl" as used herein refers to aryl in which one or more of the ring carbon atoms is replaced by a heterocyclic atom such as N, S, O or P.

The term "heteroarylalkyl" as used herein refers to a heteroaryl group appended to an alkyl group.

The term "heteroarylacylamino" as used herein refers to heteroarylC(O)NH-.

The term "heterocyclic group" or "heterocyclic" as used herein refers to any 3- or 4-membered ring containing a heteroatom selected from oxygen, nitrogen and sulfur, or a 5-, 6-, or 7-membered ring containing one, two or three nitrogen atoms; one nitrogen and one sulfur atom; or one nitrogen and one oxygen atom; wherein the 5-membered ring has 0-2 double bonds and the 6- or 7-membered ring has 0-3 double bonds; wherein the nitrogen and sulfur heteroatoms can optionally be oxidized; wherein the nitrogen heteroatom can optionally be quaternized; and, including any cyclic group in which any of the above heterocyclic rings is fused to a benzene ring or another 5-, 6- or 7-membered heterocyclic ring independently as defined above. Representative heterocyclics include indolyl, quinolyl, isoquinolyl, tetrahydroquinolyl, benzofuryl, benzothienylazetidinyl, pyrrolyl, pyrrolinyl, pyrazolyl, pyrazolinyl, pyrazolidinyl, imidazolyl, imidazolinyl, imidazolidinyl, pyridyl, piperidinyl, pyrazinyl, piperazinyl, pyrimidinyl, pyridazinyl, oxazolyl, oxazolidinyl, isoxazolyl, isoxazolidinyl, morpholinyl, thiomorpholinyl, thiazolyl, thiazolidinyl, isothiazolyl, isothiazolidinyl, benzimidazolyl, benzothiazolyl, benzoxazolyl, furyl, thienyl, trizolyl, benzothienyl, homopiperazinyl, homopiperidinyl, homomorpholinyl and the like.

The term "loweralkyl" as used herein refers to branched or straight chain, substituted or unsubstituted, alkyl groups comprising 1 to 10 carbon atoms including methyl, ethyl, propyl, isopropyl, butyl n-butyl, n-butyl, neopentyl and the like. A loweralkyl can be substiitued with halo, mercapto, nitro, amino,and the like.

The term "thioalkoxy" or "mercaptoalkoxy" as used herein refers to $-SR_{16}$ wherein R_{16} is a loweralkyl or benzyl group.

"Hydroxy-protecting group" or "O-protecting group" refers to a substituent which protects hydroxyl groups against undesirable reactions during synthetic procedures and includes, but is not limited to, substituted methyl ethers, for example, methoxymethyl, benzyloxymethyl, 2-methoxyethoxymethyl, 2-(trimethylsiyll)-ethoxymethyl, benzyl, and triphenylmethyl; tetrahydropyranyl ethers; substituted ethyl ethers, for example, 2,2,2-trichloroethyl and t-butyl; silyl ethers, for example, trimethylsilyl, t-butyldimethylsilyl and t-butyldiphenylsilyl; cyclic acetals and ketals, for example, methylene acetal, acetonide and benzylidene acetal; cyclic ortho esters, for example, methoxymethylene; cyclic carbonates; and cyclic boronates. Commonly used hydroxy-protecting groups are disclosed in

Greene, "Protective Groups In Organic Synthesis," (John Wiley & Sons, New York (1981), which is hereby incorporated by reference.

The term "N-protecting group" or "N-protected" as used herein refers to those groups intended to protect an amino group against undesirable reactions during synthetic procedures. Commonly used N-protecting groups are disclosed in Greene, "Protective Groups In Organic Synthesis," (John Wiley & Sons, New York (1981), which is hereby incorporated by reference. N-protecting groups comprise carbamates, amides including those containing hetero arylgroups, N-alkyl derivatives, amino acetal derivatives, N-benzyl derivatives, imine derivatives, enamine derivatives and N-heteroatom derivatives. Preferred N-protecting groups are formyl, acetyl, benzoyl, pivaloyl, phenylsulfonyl, benzyl, triphenylmethyl (trityl), t-butyloxycarbonyl (Boc), benzyloxycarbonyl (Cbz), nicotinoyl and the like.

Many of the terms as defined above include numerous groups (*e.g.*, arylalkyl). It is to be understood that, in the context of the present invention, the last named group in such terms is the group that is appended to the cyclic structures (*e.g.*, cyclopentane) of the Formulae I-V.

III. Pharmaceutical Compositions

In a further aspect of the present invention pharmaceutical compositions are disclosed which comprise a compound of the present invention in combination with a pharmaceutically acceptable carrier.

The present invention includes one or more compounds, as set forth above, formulated into compositions together with one or more non-toxic physiologically tolerable or acceptable diluents, carriers, adjuvants or vehicles that are collectively referred to herein as diluents, for parenteral injection, for oral administration in solid or liquid form, for rectal or topical administration, or the like. As is well known in the art, a compound of the present invention can exist in a variety of forms including pharmaceutically-acceptable salts, esters, amides and the like.

"Pharmaceutically-acceptable amide" refers to the pharmaceutically-acceptable, nontoxic amides of the compounds of the present invention which include amides formed with suitable organic acids or with amino acids, including short peptides consisting of from 1-to-6 amino acids joined by amide linkages which may be branched or linear, wherein the amino acids are selected independently from naturally-occurring amino acids, such as for

example, glycine, alanine, leucine, valine, phenylalanine, proline, methionine, tryptophan, asparagine, aspartic acid, glutamic acid, glutamine, serine, threonine, lysine, arginine, tyrosine, histidine, ornithine, and the like.

"Pharmaceutically-acceptable ester" refers to the pharmaceutically-acceptable, nontoxic esters of the compounds of the present invention which include loweralkyl esters, wherein loweralkyl is as defined above, and C5-C7-cycloalkyl esters, wherein cycloalkyl refers to cyclic saturated hydrocarbon radicals, such as cyclopentyl, cyclohexyl, and the like. Also included are aryl-alkyl esters, wherein aryl and alkyl are as defined above. Representative examples include benzyl, phenethyl, and the like.

"Pharmaceutically-acceptable salts" refers to the pharmaceutically-acceptable, nontoxic, inorganic or organic acid addition salts of the compounds of the present invention, as described in greater detail below.

The compounds of the present invention can be used in the form of pharmaceutically-acceptable salts derived from inorganic or organic acids. These salts include, but are not limited to, the following: acetate, adipate, alginate, aspartate, benzoate, benzenesulfonate, bisulfate, butyrate, camphorate, camphorsulfonate, citrate, cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, flavianate, fumarate, glucoheptonate, glycerophosphate, hemisulfate, heptonate, hexonoate, hydrochloride, hydrobromide, hydroiodide, 2-hydroxy-ethanesulfonate, lactate, maleate, methanesulfonate, nicotinate, 2-naphthalenesulfonate, oxalate, palmoate, pectinate, persulfate, 3-phenylpropionate, phosphate, picrate, pivalate, propionate, succinate, tartrate, thiocyanate, tosylate, and undecanoate.

Appropriate cationic salts are also readily prepared by conventional procedures such as treating an acid of Formula I with an appropriate amount of base, such as an alkali or alkaline earth metal hydroxide, *e.g.*, sodium, potassium, lithium, calcium, or magnesium, or an organic base such as an amine, *e.g.*, dibenzylethylenediamine, cyclohexylamine, dicyclohexylamine, triethylamine, piperidine, pyrrolidine, benzylamine, and the like, or a quanternary ammonium hydroxide such as tetramethylammonium hydroxide and the like. Also, the basic nitrogen-containing groups can be quaternized with such agents as loweralkyl halides, such as methyl, ethyl, propyl, and butyl chlorides, bromides, and iodides; dialkyl sulfates; long chain halides such as decyl, lauryl, myristyl, and stearyl chlorides, bromides and

iodides; arylalkyl halides like benzyl and phenethyl bromides, and others. Water or oil-soluble or dispersible products are thereby obtained.

The salts of the present invention can be synthesized from the compounds of Formula I which contain a basic or acidic moiety by conventional methods, such as by reacting the free base or acid with stoichiometric amounts or with an excess of the desired salt forming inorganic acid or base in a suitable solvent or various combinations of solvents.

The compositions can be administered to humans and animals either orally, rectally, parenterally, intracisternally, intravaginally, intraperitoneally, locally, or as a buccal or nasal spray.

Compositions suitable for parenteral administration can comprise physiologically acceptable sterile aqueous or non-aqueous solutions, dispersions, suspensions or emulsions and sterile powders for reconstitution into such sterile solutions or dispersions. Examples of suitable diluents include water, ethanol, polyols, suitable mixtures thereof, vegetable oils and injectable organic esters such as ethyl oleate. Proper fluidity can be maintained, for example, by the use of a coating such as lecithin, by the maintenance of the required particle size in the case of dispersions and by the use of surfactants.

Compositions can also contain adjuvants such as preserving, wetting, emulsifying, and dispensing agents. Prevention of the action of microorganisms can be insured by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, sorbic acid, and the like. It may also be desirable to include isotonic agents, for example, sugars, sodium chloride and the like. Prolonged absorption of the injectable pharmaceutical form can be brought about by the use of agents delaying absorption, for example, aluminum monostearate and gelatin.

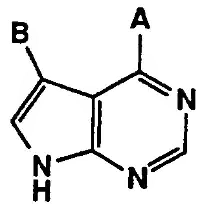
Besides such inert diluents, the composition can also include sweetening, flavoring and perfuming agents. Suspensions, in addition to the active compounds, may contain suspending agents, as for example, ethoxylated isostearyl alcohols, polyoxyethylene sorbitol and sorbitan esters, microcrystalline cellulose, aluminum metahydroxide, bentonite, agar-agar and tragacanth, or mixtures of these substances, and the like.

IV. Process of Making Adenosine Kinase Inhibitor Compounds and Synthetic Intermediates Useful in Such a Process

The present invention also relates to processes for preparing the compounds of Formula I-V and to the synthetic intermediates useful in such processes. Compounds of the present invention are prepared using standard synthetic procedures well known in the art.

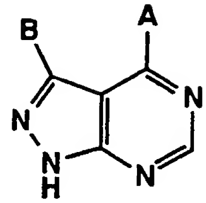
The compounds of the present invention may be synthesized by methods illustrated in Schemes 1 - 10. In accordance with Scheme 1, certain heterocyclic bases and analogs are useful starting materials. Pyrrolopyrimidines **1** (A = Cl, B = H, Cl, Br, I, CH_3,CN) have been described (L. B. Townsend, J. Med. Chem. (1990) **33**, 1984-1992; ibid, (1988) **31**, 2086-2092; Tollman, J. Am. Chem. Soc. (1969) **91**, 2102). Pyrazolopyrimidines **2** (A = NH_2, B = H, Br, I, CN, CH_2CN, Ph) have been described by (T. S. Leonova, V. G. Yashunskii; Khim. Geterotsiki. Soedin. (1982), 982-984; E. C. Taylor, J. Org. Chem. (1966) **31**, 342; Carboni, J. Am. Chem. Soc. (1958) **80**, 2838; Kobayashi, Chem. Phar. Bull. (1973) **21**, 941). 2-azapyrazolopyrimidines **4** (A = OH, NH_2, B = H) have been described (J. A. Montgomery, J. Med. Chem. (1975) **18**, 564-567; ibid, (1972) **15**, 182-189; R. K. Robins, J. Pharm. Sci. (1968) **57**, 1044. While 2-azapyrrolopyrimidines **3** have not been described, they should be available from the corresponding pyrrolopyrimidines described in Scheme 2, using the method of Montgomery (J. Med. Chem. (1972) **15**, 182-189) who used a four step method to convert substituted pyrazolopyrimidines **2** to 2-azapyrazolopyrimidines **4**.

Scheme 1.



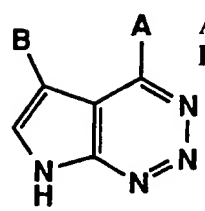
A = Cl
B = Cl, Br, I, CN, CH_3, H

(1)



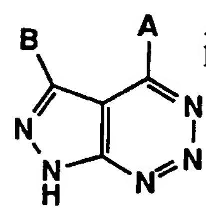
A = NH_2
B = H, Br, I, CN, CH_2CN, Ph, H

(2)
(2a, A = Cl, B = halo)



A = NH_2, OH
B = H

(3)
(3a, A = Cl, B = halo)

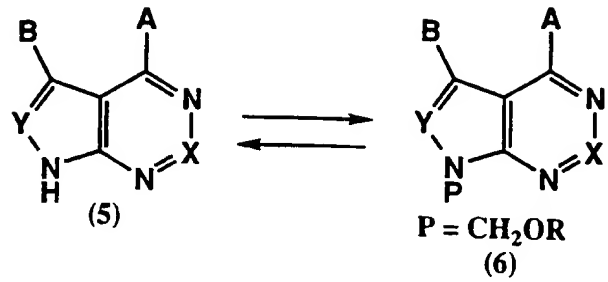


A = NH_2, OH
B = H

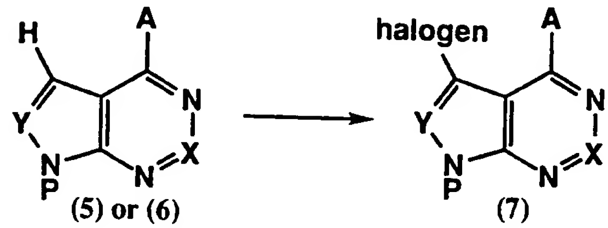
(4)
(4a, A = Cl,B = halo)

Where neccessary, the pyrrole nitrogen in the aforementioned heterocyclic bases 5 may be protected as for example the methoxymethyl ether 6 shown in Scheme 2 with methoxymethyl chloride and sodium hydride. The protecting group in 6 may be removed after synthetic transformation of the heterocyclic moiety by treatment with aqueous acid to give 5. Where synthetic intermediates 7 are required (either P = H or the protected form P = MOM), halogenation of unsubstituted (B = H) heterocycles may be effected by used of N-iodosuccinimide (NIS), N-bromosuccinimide (NBS), N-chlorosuccinimide (NCS,) or ICl as shown in Scheme 3 (Townsend, J. Med. Chem. (1988) **31**, 2086-2092; Cocuzza, Tet. Lett. (1988) **29**, 4061-4064).

Scheme 2.

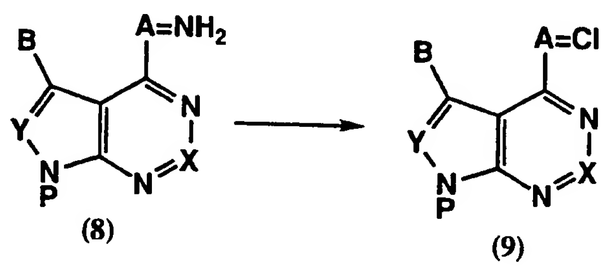


Scheme 3.



In the case where the heterocyclic base 8 (P = H or MOM) contains a substitutuent where A = NH_2, which is desired to be converted to a chlorine 9, the base may be diazotized by treatment with isoamyl nitrite, followed by treatment with hydrochloric acid to give A = Cl as shown in Scheme 4 (C. Overberger, Org. Syn. Coll. Vol. IV (1963) 182).

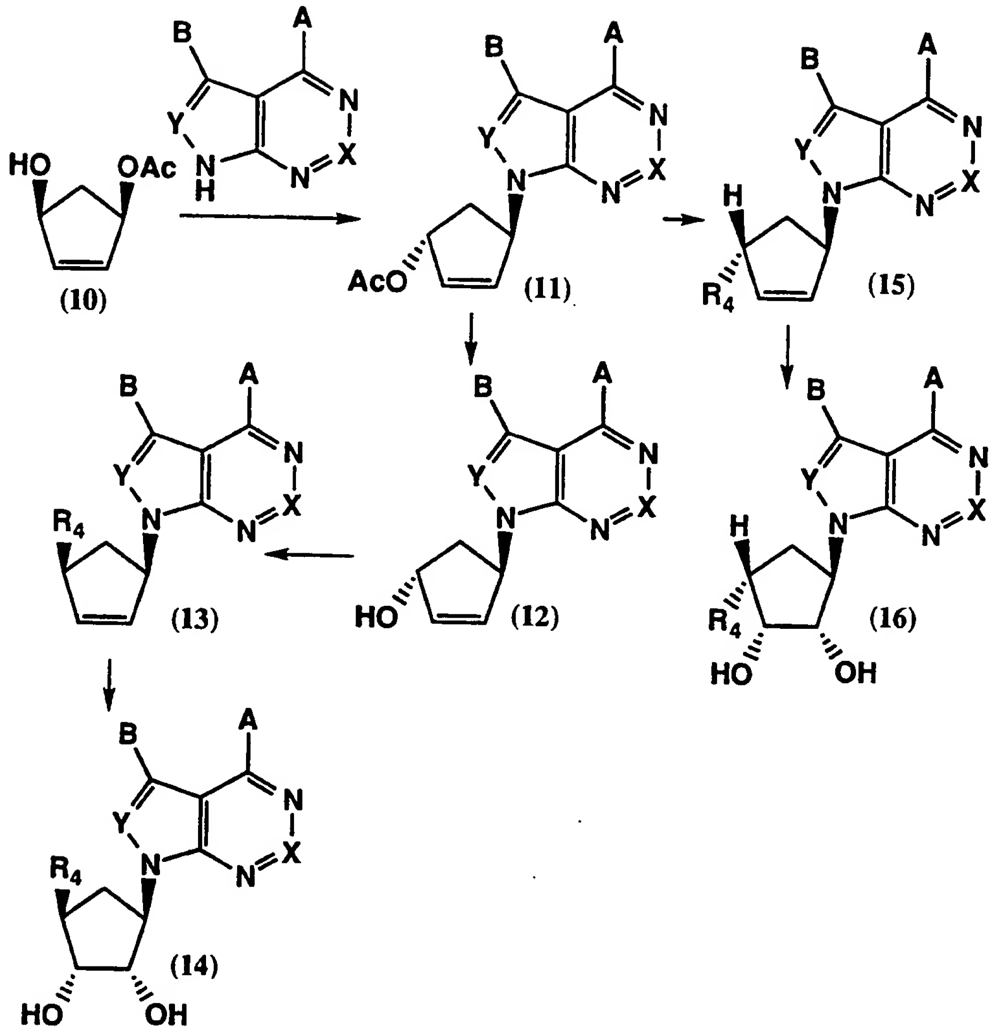
Scheme 4.



The Mitsunobu coupling of heterocyclic bases with substituted cyclopentenes like (1R,4S)-cis-4-hydroxy-2-cyclopentenyl acetate 10 (C. R. Johnson Tet. Lett. (1992) 33, 7287-7290) using triphenylphosphine and diethylazodicarboxylate to give 11 can be effected using known methods, as shown in Scheme 5 (Benner, Tet. Lett. (1991) 32, 7029-7032). The subsequently produced cyclopentenes may be deacetylated with ammonia to give alcohols 12. These may be treated with diethyl azodicarboxylate (DAST) to provide the

allylic fluoride, which after treatment with osmium tetroxide provide **13** where R_3 = F (Schneller, J. Chem. Soc., Chem. Comm. (1993) 708-709). The allylic alcohols may also be treated with nucleophiles containing acidic nitrogens (*e.g.*, bis-t-butoxycarbonylamine, phthalimide), acidic oxygens (*e.g.*, phenols), acidic sulfurs (*e.g.*, mercaptans, heteroaryl mercaptans), or phosphorus (*e.g.*, dialkylphosphine oxides) in the presence of triphenylphosphine and diethylazodicarboxylate to give **13**, using the Mitsunobu reaction. These products may in turn be treated with osmium tetroxide to give the corresponding diols **14**. Alternately, the acetate **11** may be converted to **15** by treatment with nucleophiles containing acidic nitrogens (*e.g.*, bis-t-butoxycarbonylamine, phthalimide), acidic oxygens (*e.g.*, phenols), acidic sulfurs (*e.g.*, mercaptans), or acidic phosphorus (*e.g.*, dialkylphosphites) in the presence of base and tetra-kis(triphenylphosphine)palladium, or with free base amines in the presence of tetra-kis(triphenylphosphine)-palladium (Deardorff, J. Org. Chem. (1989) **54**, 2759-2762; Genet, Tet. Lett. (1983) **24**, 2745-2748). These in turn can be treated with osmium tetroxide to give **16**.

Scheme 5.

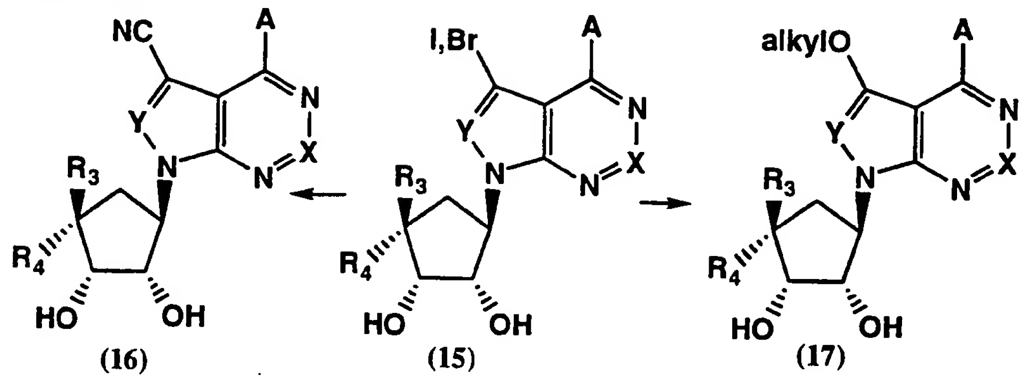


The halogenated heterocycles like **15** (B = I, Cl) can be converted to the alkylated, alkenylated, alkynylated or arylated derivatives (B = loweralkyl, aryl, heteroaryl, substituted alkynyl, substituted alkenyl) by treatment with an appropriate tributylstannyl (Stille coupling), organozinc (Negeshi modification of the Stille coupling), or sodium carbonate and an organoboronic acid (Suzuki reaction) derivative, in the presence of a catalytic amount of a palladium complex, like $Pd(PPh_3)_4$ or $PdCl_2(PPh_3)_2$.

The halogenated heterocycles like **15** can converted to cyanoheterocycles (B = CN) by treatment with copper (I) cyanide as shown in Scheme 6. Alkoxyheterocycles where B = O-alkyl can be produced by the

action of sodium alkoxides on 15, catalyzed by copper salts like copper (I) iodide.

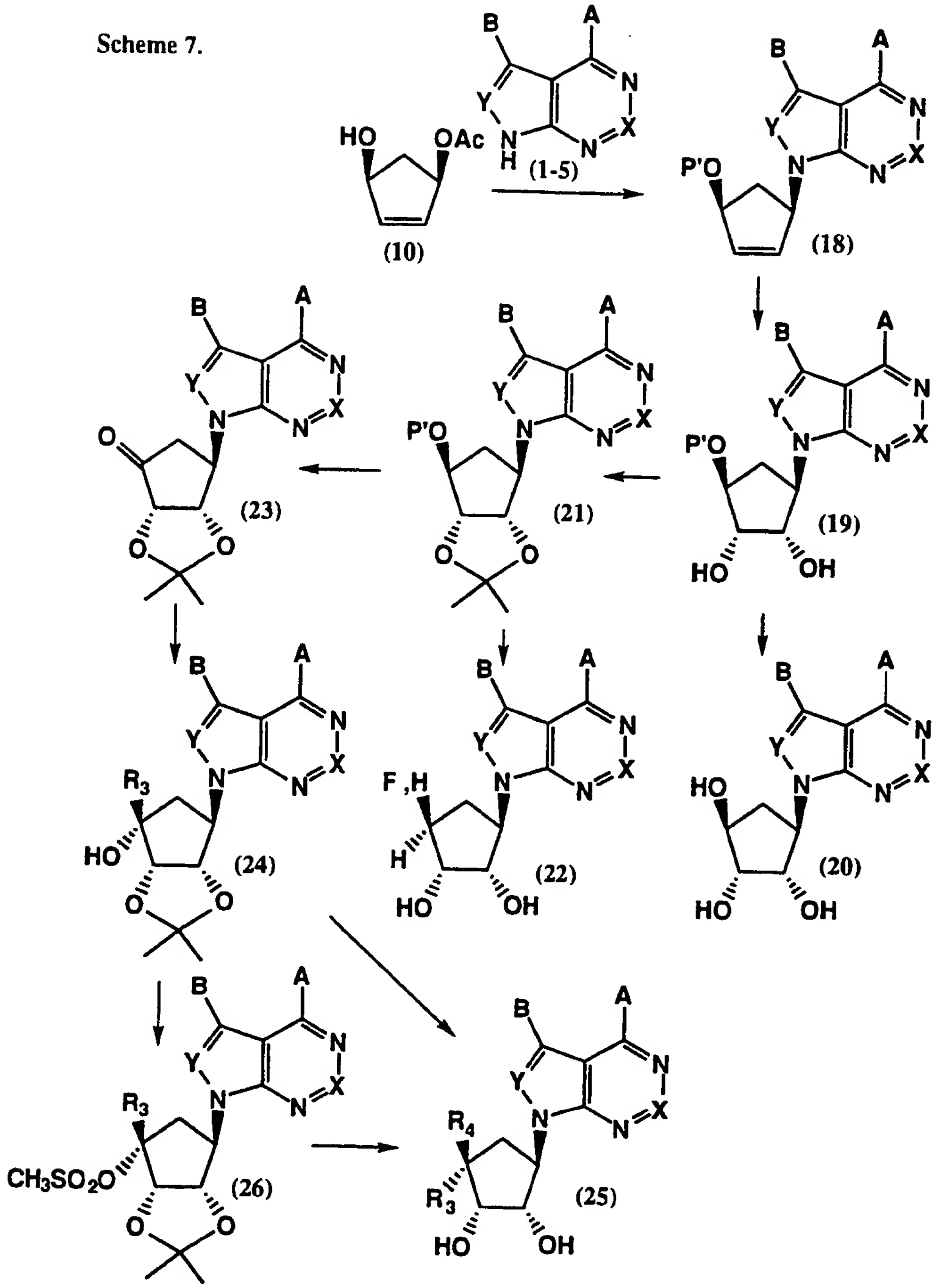
Scheme 6.



Additionally, the products of the invention can be produced by treating an allylic acetate **10** (or **10** protected with a TBS)(Greene & Wuts, in Protective Groups in Organic Synthesis, John Wiley and Sons, 199), with a heterocyclic base **(1-5)** and with a deprotonating agent such as lithium hydride, in the presence of tetrakis(triphenylphosphine)palladium (Benneche, Acta. Chem. Scan. (1992) **46**, 761-771; Benneche, Tet. Lett. (1992) **33**, 1085-1088). The resulting cyclopentenes **18** can be cis-hydroxylated with osmium tetroxide to provide **19**, then treated with a fluoride source or acid to produce the trihydroxycyclopentanes **20**. Alternatively, the hydroxyls can be protected as for example, the acetonide **21**, produced by reaction with acetone in the presence of an acid catalyst. The acetonide **21**, can then be deprotected with a fluoride source to give **21** (P' = H), and this treated with DAST, to give the fluoride **22** (R_4 = F), or deoxygenated using the Barton reaction by formation of the xanthate ester, followed by treatment with tributyltin hydride and 1,1'-azobis(isobutyronitrile (AIBN) to give **22** (R_4=H). The acetonide **21** (P'=H) can be oxidized to the ketone **23** with DMSO/oxalyl chloride/Hunig's base (Swern reaction), which can then be treated with aqueous acid to give compounds where R_3=R_4=O. Alternately, the protected ketones **23** can be reacted with nucleophiles like alkyl or aryl lithium reagents or L-selectride to provide alcohols **24** (R_3 = H, loweralkyl). These alchohols can then be treated with nucleophiles containing acidic nitrogens (bis-t-butoxycarbonylamine, phthalamide), acidic oxygens (phenols), acidic sulfurs (mercaptans), or phosphorus (dialkylphosphites) in the presence of triphenylphosphine and

diethylazodicarboxylate to give **25** using the Mitsunobu reaction as described above, then deprotected to provide compounds of the invention **25** (where R_4 = H, loweralkyl, R_3=N, O, S). Alternatively, the alcohols **24** can be converted to the methanesulfonates **26**, which can be displaced with nucleophiles containing acidic nitrogens (bis-t-butoxycarbonylamine, phthalamide), acidic oxygens (phenols), acidic sulfurs (hydrogen sulfide or substituted mercaptans), or phosphorus (dialkylphosphites) in the presence of a base like potassium carbonate, or with compounds containing nucleophilic heteroatoms (for example, hydrazine) to provide **25** (after treatment with aqueous acid). The methanesulfonates **26** can also be displaced with amines in the free base form (methylamine, aniline, imidazole) to provide **25** (after treatment with aqueous acid).

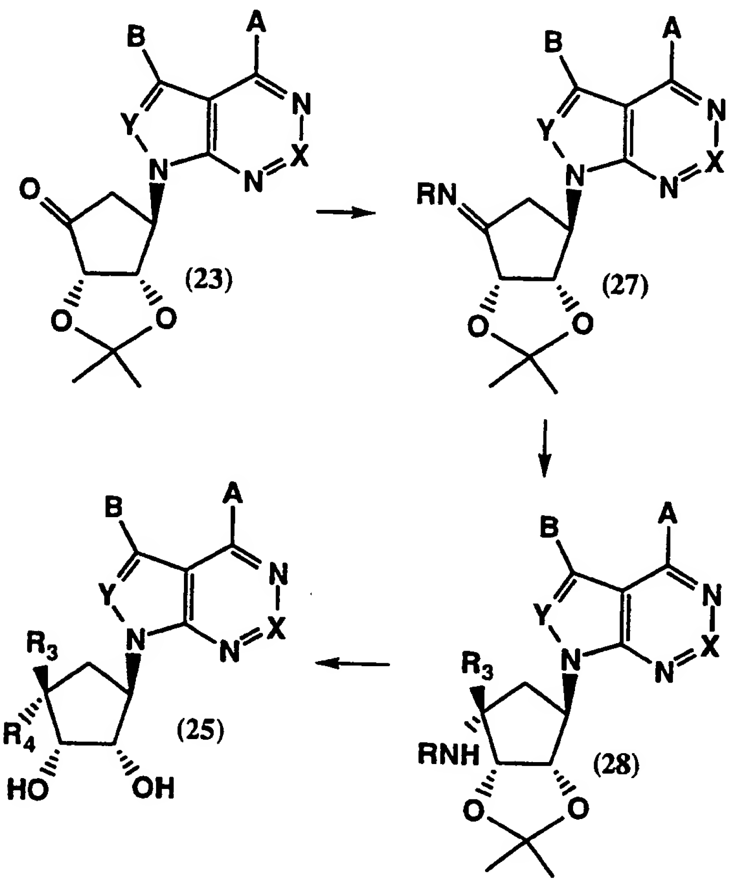
Scheme 7.



An alternative method for the synthesis of compound 25 involves condensation of ketone 23 (where A, B, X, and Y are defined in the claims) with substituted amines to give 27, as depicted in Scheme 8. This can be reduced with sodium borohydride to give 28 (R3 = H), or reacted with

organometallic reagents to give **28** (R_3 = loweralkyl). These compounds can be deprotected with aqueous acid to give compound **25** (R_3=H, loweralkyl; R_4=RNH).

Scheme 8.



In cases where A is desired to be hydroxyl or substituted oxygen, compounds where A = Cl (prepared as described above) can be treated with a metal salt of an alcohol (for example sodium methoxide) at elevated temperature, as described by Townsend (J. Med. Chem. (1988), 31, 2086-2092). In cases where A is desired to be a thioether or substituted sulfur, compounds where A = Cl (prepared as described above) can be treated with a metal salt of a mercaptan (for example the sodium salt of ethanethiol) at elevated temperature, as described above. In cases where A is desired to be amine, or substituted amine, compounds where A = Cl (prepared as described above)

can be treated with ammonia or the amine (for example methylamine or morpholine) at elevated temperature, as described above.

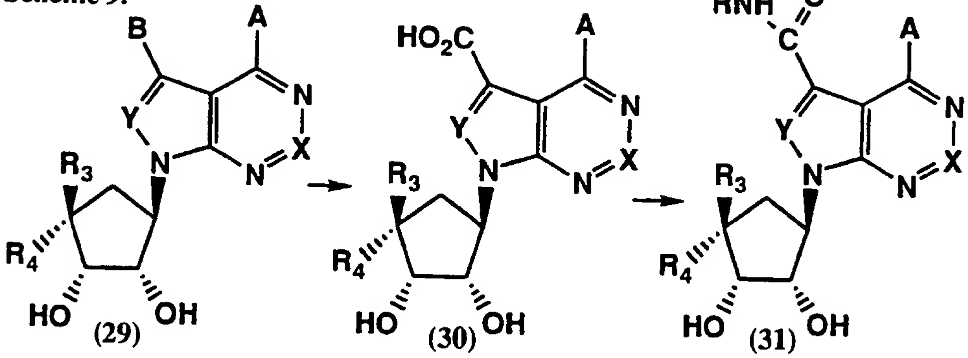
In cases where A is desired to be a urea, compounds where A = NH_2 (synthesized as described above) can be prepared by treatment with an sodium isocyanide in acid, or with an isocyanate (for example, methyl isocyate) in basic solution. In cases where A is desired to be a carbamate, compounds where A = NH_2 (synthesized as described above) can be prepared by treatment with a substituted chloroformate ester (for example, phenyl chloroformate) in basic solution. In cases where A is desired to be an amide, compounds where A = NH_2 (synthesized as described above) can be prepared by treatment with a substituted acyl chloride (for example benzoyl chloride) in pyridine. In cases where A is desired to be a halogen other than chlorine, compounds where A = Cl (synthesized as described above) can be prepared by treatment with the corresponding mineral acid (for example hydrobromic acid), or by treatment with the copper(I) salt of the halide, for example (copper(I)iodide) at elevated temperature.

In cases where B is desired to be an alkyl group, compounds **25** where B = I or Br, can be subjected to the Negishi modification of the Stille coupling. In this case, the halogenated compound is treated with an alkyl zinc reagent in the presence of a catalytic amount of a palladium complex, like $Pd(PPh_3)_4$ or $PdCl_2(PPh_3)_2$. In cases where B is desired to be aryl, heteroaryl, alkyl-substituted alkenyl, or aryl-substituted alkenyl, the compounds **25** where B = I or Br, can be subjected to the Stille reaction. In this case, the halogenated compound is treated with a appropriately substituted organostannane or sodium carbonate and an organoboronic acid reagent, in the presence of a catalytic amount of a palladium complex, like $Pd(PPh_3)_4$ or $PdCl_2(PPh_3)_2$.

The halogenated heterocycles **29** (where B=Br, I, and A, X, Y, R_3,R_4) can also be converted to compounds, where B = CO_2CH_3, by treatment of **29** with a Pd catalyst in methanol under an atmosphere of carbon monoxide (Bergstrom, J. Org. Chem. (1981) 46, 1423-1431). Sodium hydroxide induced hydrolysis gives the acid **30**, which can be converted to the corresponding amides **31** by treatment with diphenylphoryl azide or carbonyl diimidazole, followed by treatment with an amine as shown in Scheme 9 (Ann. Reviews in Biochemistry, (1970) 39, 841). In cases where protection of the 2',3' hydroxyls (R_1=R_2=OH) is required, **29** can be protected as the acetonide as described for compound **21**, and following synthetic transformation,

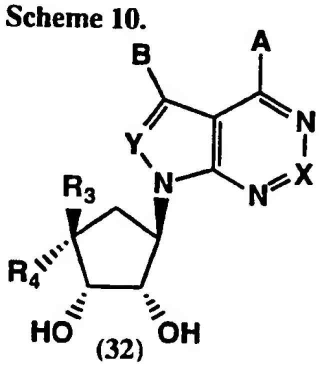
deprotected to give **31**, as described for the transformation of compound **24** into compound **25**.

Scheme 9.



In cases where B is desired to be an alkoxy group, compounds **29** where B = I or Br, can be treated with an alkoxide salt and a catalytic amount of a copper salt like copper(I)iodide at elevated temperature. In cases where B is desired to be a cyano group, compounds **29** where B = I or Br, can be treated with copper(I)cyanide at elevated temperature.

Scheme 10.



In cases where R3 or R4 are desired to be substituted nitrogen, the compounds **32**, where R3 or R4 are NH2 (prepared as descibed above), can reductively alkylated with aldehydes (for example, formaldehyde) in the presence of sodium cyanoborohydride (Borcht reduction), or in the presence of formic acid (Eschweiler-Clark reaction). In cases where R3 or R4 are desired to be substituted amino, compounds where R3 or R4 are NH2 can be reacted with electrophilic halogenated heterocycles (like 3,6-dichloropyridazine), with

electrophilic haloaromatics (like 2-fluoronitrobenzene), or with substituted alkyl halides (like benzyl chloride).

In cases where R_3 or R_4 is desired to be a urea, compounds where R_3 or $R_4 = NH_2$ (synthesized as described above) can be treated with potassium cyanate in acid (L. P. Walls J. Chem. Soc. (1946), 1031), or with an isocyanate (for example, methyl isocyanate) in basic solution (T. L. Hough,, *et al.* J. Heterocyclic Chem. (1986) **23**, 1125). In cases where R_3 or R_4 is desired to be a carbamate, compounds where R_3 or $R_4 = NH_2$ (synthesized as described above) can be prepared by treatment with a substituted chloroformate ester (for example, phenyl chloroformate) in basic solution. In cases where R_3 or R_4 is desired to be an amide, compounds where R_3 or $R4 = NH_2$ (synthesized as described above) can be prepared by treatment with a substituted acyl chloride (for example, propionyl chloride) in pyridine or basic solution. In cases whereR_3 or R_4 is desired to be a sulfonamide, compounds where R_3 or $R_4 = NH_2$ (synthesized as described above) can be prepared by treatment with a substituted sulfonyl chloride (for example methanesulfonyl chloride) in basic solution. In cases where R_3 or R_4 is desired to be a sulfamate, compounds where R_3 or R_4 = OH (synthesized as described above) can be prepared by treatment with H_2NSO_2Cl in the presence of a base (for example, sodium hydride) as described by Vince (J. Med. Chem. (1992) **35**, 3991-4000).

In cases where R_1 and R_2 are desired to be for instance O-acyl or O(C=O)O, the compounds where R_1 and R_2 are OH can be treated with an acyl chloride in pyridine to provide R_1,R_2=Oacyl, or with carbonyl diimidazole in pyridine or DMF to provide the carbonate where R_1, R_2 is O(C=O)O.

Compounds where $R_1 = R_2 = H$ can be prepared by hydrogenating the corresponding olefinic compounds with platinum oxide and hydrogen gas. The compounds where $R_1 = H$, $R_2 = OH$ and $R_1 = OH$, $R_2 = H$ can be prepared from the corresponding olefinic compounds by hydroboration using borane followed by oxidation with N-methylmorpholine oxide.

One of ordinary skill in the art will readily appreciate that the generalized Schemes 1-10 set forth above are exemlary and that similar procedures can be used to prepare compounds having other substituents, stereochemistry and other like modifications.

A detailed description of the synthesis of numerous inhibitor compounds of the present invention is set forth hereinafter in the Examples.

The present invention also provides synthetic intermediates useful in making the inhibitor compound of the present invention. Certain intermediates in the production of compounds of the present invention likely have use as prodrugs.

The term "prodrug" refers to compounds that are rapidly transformed *in vivo* to yield the parent compounds of Formula (I), as for example, by hydrolysis in blood. T. Higuchi and V. Stella provide a thorough discussion of the prodrug concept in Prodrugs as Novel Delivery Systems, Vol. 14 of the A.C.S. Symposium Series, American Chemical Society (1975). Examples of esters useful as prodrugs for compounds containing carboxyl groups can be found on pages 14-21 of Bioreversible Carriers in Drug Design: Theory and Application, edited by E.B. Roche, Pergamon Press (1987).

The term "prodrug ester group" refers to any of several ester-forming groups that are hydrolyzed under physiological conditions. Examples of prodrug ester groups include pivoyloxymethyl, acetoxymethyl, phthalidyl, indanyl and methoxymethyl, as well as other such groups known in the art.

Exemplary such compounds are:

N7-((1'R,2'S,3'S,4'S)-2',3'-dihydroxy-4'-(t-butyldimethylsilyloxy)-cyclopentyl)-4-chloro-pyrrolopyrimidine;

N7-((1'R,2'S,3'R,4'S)-2',3',4'-triacetoxycyclopentyl)-4-chloro-5-phenyl-pyrrolopyrimidine;

N7-((1'R,2'S,3'R,4'S)-2',3',4'-triacetoxyclopentyl)-4,5-bis-phenylacetylenyl-pyrrolopyrimidine and N7-((1'R,2'S,3'R,4'S)-2',3',4'-tri-acetoxycyclopentyl)-4-chloro-5-phenylacetylenyl-pyrrolopyrimidine;

N7-((1'R,2'S,3'R,4'S)-2',3',4'-triacetoxycyclopentyl)-4,5-dichloro-pyrrolopyrimidine;

N7-((1'R,2'S,3'R,4'S)-2',3'-dihydroxy-4'-(trifluoroacetyl)amino-cyclopentyl)-4-chloro-5-iodo-pyrrolopyrimidine and N7-((1'R,2'S,3'R,4'S)-2',3'-dihydroxy-4'-(trifluoroacetyl)amino-cyclopentyl)-4-hydroxy-5-iodo-pyrrolopyrimidine;

N7-((1'R,2'S,3'R,4'S)-2',3'-O-(2"-oxo-1",3"-dioxayl)-4'-amino-cyclopentyl)-4-chloro-5-iodo-pyrrolopyrimidine;

N7-((1'R,2'S,3'R,4'S)-2',3'-diacetoxy-4'-(acetyl)amino-cyclopentyl)-4-chloro-5-iodo-pyrrolopyrimidine;

N7-((1'R,2'S,3'R,4'S)-2',3'-O-(2"-oxo-1",3"-dioxalyl)-4'-(acetyl)amino-cyclopentyl)-4-chloro-5-iodo-pyrrolopyrimidine and N7-((1'R,2'S,3'R,4'S)-2',3'-

O-(2″-oxo-1″,3″-dioxalyl)-4′-(acetyl)amino-cyclopentyl)-4-hydroxy-5-iodo-pyrrolopyrimidine;

N7-((1′R,2′S,3′R,4′S)-2′,3′-dihydroxy-4′-(acetyl)amino-cyclopentyl-4-chloro-5-iodo-pyrrolopyrimidine;

N7-((1′R,2′S,3′R,4′S)-2′,3′-dihydroxy-4′-(acetyl)amino-cyclopentyl-4-amino-5-iodo-pyrrolopyrimidine;

N7-((1′R,2′S,3′R,4′S)-2′,3′-dihydroxy-4′-(3″-nicotinoyl)amino-cyclopentyl)-4-chloro-5-iodo-pyrrolopyrimidine; and

N7-((1′R,2′S,3′R,4′S)-2′,3′-diacetoxy-4′-(acetyl)amino-cyclopentyl)-4-amino-5-iodo-pyrrolopyrimidine.

V. Process of Inhibiting Kinase

In yet another aspect of the present invention a process of inhibiting adenosine kinase is disclosed. In accordance with that process, an adenosine kinase enzyme is exposed to an effective inhibiting amount of an adenosine kinase inhibitor compound of the present invention. Preferred such compounds for use in the process are the same as set forth above. Means for determining an effective inhibiting amount are well known in the art.

The adenosine kinase to be inhibited can be located *in vitro, in situ or in vivo*. Where the adenosine kinase is located *in vitro*, adenosine kinase is contacted with the inhibitor compound, typically by adding the compound to an aqueous solution containing the enzyme, radiolabeled substrate adenosine, magnesium chloride and ATP. The enzyme can exist in intact cells or in isolated subcellular fractions containing the enzyme. The enzyme is then maintained in the presence of the inhibitor for a perod of time and under suitable physiological conditions. Means for determining maintainence times are well known in the art and depend inter alia on the concentrations of enzyme and the physiological conditions. Suitable physiological conditions are those necessary to maintain adenosine kinase viability and include temperature, acidity, tonicity and the like. Inhibition of adenosine kinase can be performed, by example, according to standard procedures well known in the art (Yamada, *et al., Comp. Biochem. Physiol.* 1982, **71B**: 367-372).

Where the adenosine kinase is located *in situ* or *in vivo*, is typically administered to a fluid perfusing the tissue containing the enzyme. That fluid can be a naturally occuring fluid such as blood or plasma or an artificial

fluid such as saline, Ringer's solution and the like. A process of inhibiting adenosine kinase *in vivo* is particularly useful in mammals such as humans. Administering an inhibitor compound is typically accomplished by the parenteral (*e.g.*, intravenous injection or oral) administration of the compound. The amount administered is an effective inhibiting or therapeutic amount.

Compounds of the present invention inhibit adenosine kinase activity *in vitro* and *in vivo*. *In vitro* adenosine kinase activity can be measured using any of the standard procedures well known in the art. By way of example, cells containing adenosine kinase, such as IMR-32 human neuroblastoma cells, are cultured in the presence and absence of an inhibitor. Inhibition is measured as the ability to inhibit phosphorylation of endogenous or externally applied ^{14}C-adenosine by these cells. The cells can be intact or broken. The specificity of adenosine kinase inhibitory activity is determined by studying the effects of inhibitors on adenosine A1 and A2a receptor bindng, adenosine deaminase activity and adenosine transport.

By a "therapeutically-effective amount" of the compound of the invention is meant a sufficient amount of the compound to treat disorders, at a reasonable benefit/risk ratio applicable to any medical treatment. It will be understood, however, that the total daily usage of the compounds and compositions of the present invention is to be decided by the attending physician within the scope of sound medical judgment. The specific therapeutically-effective dose level for any particular patient will depend upon a variety of factors including the disorder being treated and the severity of the disorder; activity of the specific compound employed; the specific composition employed; the age, body weight, general health, gender and diet of the patient; the time of administration, route of administration, and rate of excretion of the specific compound employed; the duration of the treatment; drugs used in combination or coincidental with specific compound employed; and the like factors well known in the medical arts and well within the capabilities of attending physicians.

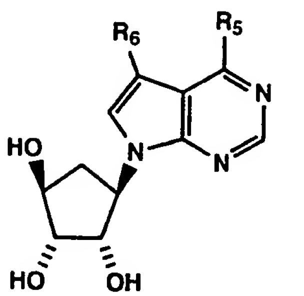
Compounds of the present invention are effective in inhibiting a adenosine kinase activity *in vivo*. Numerous animal models for studying adenosine kinase activity and the affects of inhibiting such activity are well known in the art. By way of example, adenosine kinase inhibitors have been reported to protect rodents (*e.g.*, mice and rats) from seizures induced by the

subcutaneous administration of pentylenetetrazol (PTZ). Typically the rodents are injected with various doses of a given inhibitor followed at various times by the subcutaneous administration of from about 10 to about 500 milligrams per kilogram of PTZ. The injected animals are then observed for the onset of seizures.

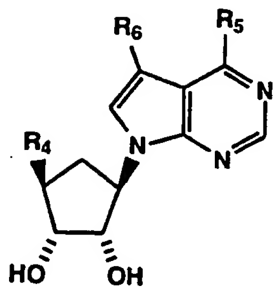
Numerous other animal models of adenosine kinase activity have been described [See, *e.g.*, Davies,, *et al., Biochem. Pharmacol.*, **33**:347-355 (1984); Keil, *et al., Eur. J. Pharmacol.*, **271**:37-46 (1994); *Murray, et al., Drug Development Res.*, **28**:410-415 (1993)].

Numerous inhibitor compounds of the present invention were tested *in vitro* and found to inhibit adenosine kinase activity. The results of some representative studies are shown below in Tables 1 and 2.

Table 1



R_5	R_6	IC_{50} (μM)
Cl	Cl	0.090
Cl	I	0.010
NH_2	I	0.013
NHPh	I	0.10
Cl	Ph	0.045
NH_2	Ph	0.20
NHPh	Ph	0.003
PhC≡C	PhC≡C	0.015
Cl	PhC≡C	0.10
NH_2	PhC≡C	0.23
NH_2	$PhCH_2CH_2$	0.30



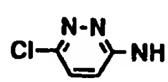
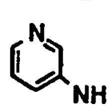
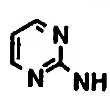
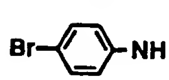
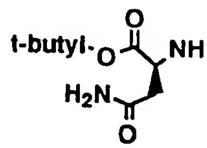
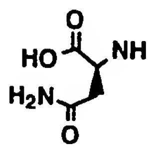
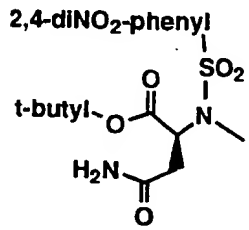
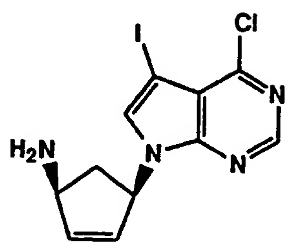
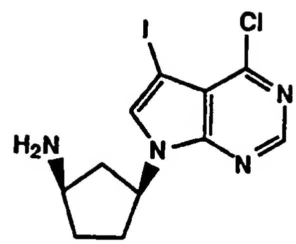
R_4	R_5	R_6	IC_{50} (μM)
NH_2	Cl	I	0.000035
NH_2	NH_2	I	0.000080
$N(Boc)_2$	Cl	I	>1
NHBoc	NH_2	I	0.015
CH_3NH	Cl	CH_3	0.3
$(CH_3)_2N$	Cl	I	0.02
NH_2	NHPh	Ph	0.035
NH_2	C≡C-Ph	C≡C-Ph	0.004
	NH_2	I	0.020
	Cl	I	0.070
	NH_2	I	0.038
	Cl	I	0.015

Table 1 (Continued)

t-buOCOCH$_2$NH	Cl	I	0.028
HO$_2$CCH$_2$NH	Cl	I	0.15
	Cl	I	0.20
	Cl	I	0.048
	Cl	I	0.35

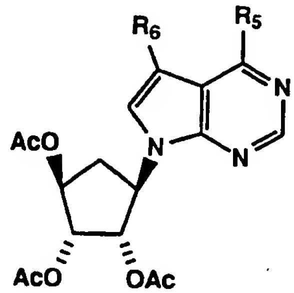


IC$_{50}$ = 3 μM

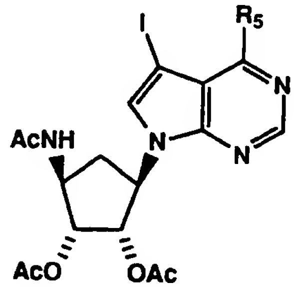


IC$_{50}$ = 0.33 μM

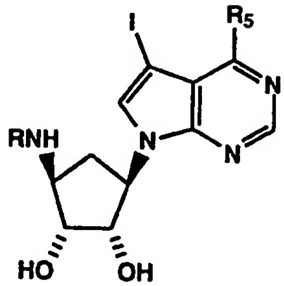
Table 2



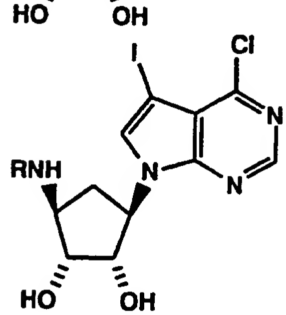
R_5	R_6	IC_{50} (μM)
Cl	Cl	>10
Cl	I	>100
Cl	Ph	>100
PhC≡C	PhC≡C	>10



R_5	IC_{50} (μM)
Cl	>10



R_5	R	IC_{50} (μM)
Cl	CF_3CO	0.11
OH	CF_3CO	0.20
Cl	CH_3CO	0.35
NH_2	CH_3CO	0.16
NH_2	NHBoc	0.15



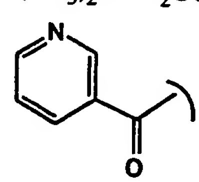
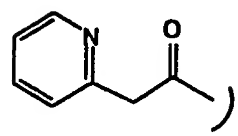
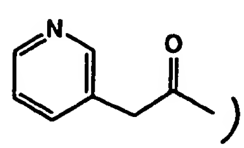
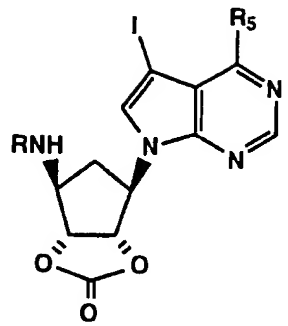
R	IC_{50} (μM)
CH_3OCO	0.30
NH_2CH_2CO	0.032
$(CH_3)_2NCH_2CO$	0.48
	0.005
	0.175
	0.25

Table 2 (Continued)



R	R_5	IC_{50} (μM)
H	Cl	0.0025
CH_3CO	Cl	6.3
CH_3CO	OH	4.0

VI. Process of Treating Cerebral Ischemia, Epilepsy, Nociperception (Nociception), Inflammation including conditions such as Septic Shock due to Sepsis Infection

In yet another aspect of the present invention a method of treating cerebral ischemia, epilepsy, nociperception or nociception, inflammation including conditions such as septic shock due to sepsis infection in a human or lower mammal is disclosed, comprising administering to the patient a therapeutically effective amount of a compound.

Alterations in cellular adenosine kinase activity have been observed in certain disorders. Adenosine kinase activity was found to be decreased, relative to normal liver, in a variety of rat hepatomas: activity of the enzyme giving a negative correlation with tumor growth rate (Jackson, *et al., Br. J. Cancer*, 1978, **37**: 701-713). Adenosine kinase activity was also diminished in regenerating liver after partial hepatectomy in experimental animals (Jackson, *et al., Br. J. Cancer*, 1978, **37**: 701-713). Erythrocyte Adenosine kinase activity was found to be diminished in patients with gout (Nishizawa, *et al., Clin. Chim. Acta* 1976, **67**: 15-20). Lymphocyte adenosine kinase activity was decreased in patients infected with the human immunodeficiency virus (HIV) exhibiting symptoms of AIDS, and increased in asymptomatic HIV-seropositive and HIV-seronegative high-risk subjects, compared to normal healthy controls (Renouf, *et al., Clin. Chem.* 1989, **35**: 1478-1481). It has been suggested that measurement of adenosine kinase activity may prove useful in monitoring the clinical progress of patients with HIV infection (Renouf, *et al., Clin. Chem.* 1989, **35**: 1478-1481). Sepsis infection may lead to a systemic inflammatory syndrome (SIRS), characterized by an increase in cytokine production, neutrophil accumulation, hemodynamic effects, and tissue damage or death. The ability of adenosine kinase inhibitor to elevate

adenosine levels in tissues has been demonstrated to ameliorate syndrome symptoms, due to the know anti-inflammatory effects of adenosine. (Firestein, et al., *J. of Immunology*, 1994, pp. 5853-5859). The ability of adenosine kinase inhibitors to elevate adenosine levels is expected to alleviate pain states, since it has been demonstrated that administration of adneosine or its analogs results in antinociception or antinociperception. (Swaynok, et al., *Neuroscience*, 1989, 32: No. 3, pp. 557-569).

The following Examples illustrate preferred embodiments of the present invention and are not limiting of the specification and claims in any way.

EXAMPLE 1: Synthesis of **(1R,4S)-cis-4-(t-butyldimethylsilyloxy)-1-acetoxy-2-cyclopentene**: A mixture of 710 mg of (1R,4S)-cis-4-hydroxy-2-cyclopentenyl acetate, 1.21 g of t-butyldimethylsilylchloride, and 1.09 g of imidazole in 1.7 mL of dimethylformamide was stirred at 25 °C for six hours, then poured into a mixture of ethyl acetate/hexane and washed with sodium phosphate buffer (pH 7). The organic phase was dried ($MgSO_4$), concentrated *in vacuo*, and purified by flash chromatography, eluting with ethyl acetate/hexane, to give 1.08 g of a thin clear oil. Mass spectrum: [M+H] m/z 257. Analysis: ($C_{13}H_{24}SiO_3$) found: C 60.90, H 9.43. $[\mu]_D^{25}$= -0.80 ° (c = 1.8, CH_2Cl_2).

EXAMPLE 2: Synthesis of **N7-((1'R,4'S)-cis-4'-(t-butyldime-thylsilyloxy)-2'-cyclopentenyl)-4-chloro-pyrrolopyrimidine**: A mixture of 216 mg of 4-chloropyrrolopyrimdine (L. B. Townsend reference), 297 mg of (1R,4S)-cis-4-(t-butyldimethylsilyloxy)-1-acetoxy-2-cyclopentene, 11.3 mg of lithium hydride, 225 mg of triphenylphosphine, and 129 mg of tris(dibenzylidineacetone)dipalladium (0) (Aldrich) in 1.4 mL of dimethylsulfoxide was heated with stirring under nitrogen at 70 °C for 18 hours, then poured into ethyl acetate and washed with sodium phosphate buffer (pH 7). The organic phase was dried ($MgSO_4$), and concentrated *in vacuo*. The resulting oil was dissolved in CH_2Cl_2/hexane and purified by flash chromatate/hexane, to give the title compound as a clear oil. Mass spectrum: [M+H] m/z 350. Analysis: ($C_{17}H_{24}SiClN_3O$·0.2 ethyl acetate) found: C 57.82, H 6.66, N 11.10. $[a]_D^{25}$= +35.94 ° (c = 1.1, CH_2Cl_2).

EXAMPLE 3: Synthesis of **N7-((1'R,2'S,3'R,4'S)-2',3',4'-trihydroxy-cyclopentyl)-4-chloro-5-iodo-pyrrolopyrimidine**: A mixture of 250 mg of N7-((1'R,2'S,3'R,4'S)-2',3',4'-triacetoxycyclopentyl)-4-chloro-5-iodo-pyrrolopyrimidine in methanol was saturated with ammonia and stirred under nitrogen at 25 °C for 60 hours. Concentration *in vacuo* gave a white solid which was recrystallized from ethanol/water to give 140 mg of clear plates, mp 206-207 °C. Mass spectrum: [M+H] m/z 396. Analysis: $C_{11}H_{11}N_3O_3ICl$ found: C 33.68, H 2.61, N 10.55. $[a]_D^{25}$= -40.12 ° (c = 0.33, CH_3OH).

EXAMPLE 4: Synthesis of **N7-((1'R,2'S,3'S,4'S)-2',3'-dihydroxy-4'-(t-butyldimethylsilyloxy)-cyclopentyl)-4-chloro-pyrrolopyrimidine**: A mixture of 312 mg of N7-((1'R,4'S)-cis-4'-(t-butyldimethylsilyloxy)-2'-cyclopentenyl)-4-chloro-pyrrolopyrimidine, 1.1g of N-methylmorpholine-N-oxide, and 2 mL of a 2.5% solution of osmium tetroxide solution in t-butanol, in 3 mL of t-butanol and 2 mL of tetrahydrofuran was stirred under nitrogen at 8 °C for 30 minutes, then poured into ethyl acetate and washed with with sodium phosphate buffer (pH 7) and saturated NaCl solution. The organic phase was dried (Na_2SO_4), and concentrated *in vacuo*. The resulting oil was purified by flash chromatography, eluting with ethanol/CH_2Cl_2, to give thetitle compound as a white solid, mp 164-165 °C. Mass spectrum: [M+H] m/z 384. Analysis: ($C_{17}H_{26}N_3O_3SiCl$) found: C 53.23, H 6.91, N 10.93. $[a]_D^{25}$= +9.58 ° (c = 0.7, CH_2Cl_2).

EXAMPLE 5: Synthesis of **N7-((1'R,2'S,3'R,4'S)-2',3',4'-triacetoxy-cyclopentyl)-4-chloro-pyrrolopyrimidine**: A mixture of 947 mg of N7-((1'R,2'S,3'S,4'S)-2',3'-dihydroxy-4'-(t-butyldimethylsilyloxy)-cyclopentyl)-4-chloro-pyrrolopyrimidine, 3 mL of a 1-M solution of tetra-(n-butyl)ammonium fluoride (TBAF) in THF, was stirred under nitrogen at 25 °C for 18 hours, then another 1 mL of 1-M TBAF solution was added. After six hours, the reaction was concentrated *in vacuo*, and 15 mL of pyridine, 63 mg of 4-dimethylaminopyridine (DMAP), and 1 mL of acetic anhydride were added. After stirring at 25 °C for 8 hours, the mixture was quenched with 0.5 mL of water and poured into ethyl acetate/hexane and whashed with sodium phosphate buffer (pH 7), and water. The organic phase was dried (Na_2SO_4), and concentrated *in vacuo*. The resulting oil was purified by flash chromatography, eluting with ethyl acetate/hexane, followed by dissolving in

chloroform and concentration to give 994 mg of a clear glass. Mass spectrum: [M+H] m/z 396. Analysis: ($C_{17}H_{18}N_3O_6Cl \cdot$ 0.33 chloroform) found: C 47.88 H 4.17, N 9.55.

EXAMPLE 6: Synthesis of **N7-((1'R,2'S,3'R,4'S)-2',3',4'-triaceto-xycyclopentyl)-4-chloro-5-iodo-pyrrolopyrimidine**: A mixture of 749 mg of N7-((1'R,2'S,3'R,4'S)-2',3',4'-triacetoxycyclopentyl)-4-chloro-pyrrolopyrimidine, 483 mg of sodium carbonate, 2.09 mL of a 1-M solution of ICl in CH_2Cl_2, and 4 mL CH_2Cl_2 was stirred under nitrogen at 25 °C for 18 hours. The mixture was poured into ethyl acetate and washed with a mixture of 10% sodium thiosulfate and saturated $NaHCO_3$. The organic phase was dried ($MgSO_4$), and concentrated *in vacuo*. The resulting oil was purified by flash chromatography, eluting with ethyl acetate/hexane, to give 729 mg of a white powder, mp 142-143 °C. Mass spectrum: [M+H] m/z 522. Analysis: $C_{17}H_{17}N_3O_6ICl$ found: C 39.35, H 3.21, N 7.97. $[a]_D^{25}$= +0.55 ° (c = 0.97, CH_3OH).

EXAMPLE 7: Synthesis of **N7-((1'R,2'S,3'R,4'S)-2',3',4'-triacetoxy-cyclopentyl)-4-chloro-5-phenyl-pyrrolopyrimidine**: A mixture of 280 mg of N7-((1'R,2'S,3'R,4'S)-2',3',4'-triacetoxycyclopentyl)-4-chloro-5-iodo-pyrrolopyrimidine, 33 mg of triphenylarsine, 25 mg of tris(dibenzylidineacetone)dipalladium (0), and 154 mg of phenyltrimethylstannane in 3.5 mL of DMF was stirred under nitrogen at 65 °C for 19 hours. The mixture was poured into ethyl acetate and washed with water. The organic phase was dried ($MgSO_4$), and concentrated *in vacuo*. The resulting oil was purified by flash chromatography, eluting with ethyl acetate/hexane, to give 205 mg of a clear glass. Mass spectrum: [M+H] m/z 472.

EXAMPLE 8: Synthesis of **N7-((1'R,2'S,3'R,4'S)-2',3',4'-trihydroxycyclopentyl)-4-amino-5-iodo-pyrrolopyrimidine**: A solution of 67 mg of N7-((1'R,2'S,3'R,4'S)-2',3',4'-trihydroxycyclopentyl)-4-chloro-5-iodo-pyrrolopyrimidine in methanol at 0 °C was saturated with ammonia, then heated in a sealed tube at 112 °C for 60 hours. Concentration *in vacuo* gave a black residue which was dissolved in DMF/methanol and purified by flash chromatography, eluting with methanol/ethyl acetate to give 46 mg of of a white powder, which was recrystallized from methanol/water to give long white needles, mp 233-235 °C (dec.). Mass spectrum: [M+H] m/z 377. Analysis:

$C_{11}H_{13}N_4O_3I$·(0.1 water) found: C 34.99, H 3.46, N 14.63. $[a]_D^{25}$= -36.00 ° (c = 0.20, CH_3CH_2OH).

EXAMPLE 9: Synthesis of **N7-((1'R,2'S,3'R,4'S)-2',3',4'-trihydroxycyclopentyl)-4-chloro-5-phenyl-pyrrolopyrimidine**: A solution of 85 mg of N7-((1'R,2'S,3'R,4'S)-2',3',4'-triacetoxycyclopentyl)-4-chloro-5-phenyl-pyrrolopyrimidine in methanol at 0 °C was saturated with ammonia, then stirred at 25 °C for 24 hours in a sealed flask. Concentration *in vacuo* gave a semisolid mass which was purified by flash chromatography, eluting with ethanol/ethyl acetate to give 57 mg of of a white foam. Mass spectrum: [M+H] m/z 346. Analysis: $C_{17}H_{16}N_3O_3Cl$·(0.5 water)(0.25 ethyl acetate) found: C 57.41, H 5.00, N 11.03. $[a]_D^{25}$= -44.19 ° (c = 0.5, CH_3OH).

EXAMPLE 10: Synthesis of **N7-((1'R,2'S,3'R,4'S)-2',3',4'-tri-hydroxycyclopentyl)-4-(phenyl)amino-5-phenyl-pyrrolopyrimidine**: A solution of 102 mg of N7-((1'R,2'S,3'R,4'S)-2',3',4'-triacetoxycyclopentyl)-4-chloro-5-phenyl-pyrrolopyrimidine, 122 mg of triethylamine, and 179 mg of aniline in ethanol was stirred at 135 °C for 20 hours in a sealed tube. Concentration *in vacuo* gave a brown glass which was purified by flash chromatography, eluting with ethanol/ethyl acetate to give 29 mg of a white powder. This was recrystallized from methanol to give white needles, mp 193-195 °C. Mass spectrum: [M+H] m/z 403. Analysis: $C_{23}H_{22}N_4O_3$·(1.0 water) found: C 65.67, H 5.88, N 13.42. $[a]_D^{25}$= -51.39 ° (c = 0.25, 50% CH_2Cl_2/CH_3OH).

EXAMPLE 11: Synthesis of **N7-((1'R,2'S,3'R,4'S)-2',3',4'-tri-hydroxycyclopentyl)-4-amino-5-phenyl-pyrrolopyrimidine**: A solution of 102 mg of N7-((1'R,2'S,3'R,4'S)-2',3',4'-triacetoxycyclopentyl)-4-chloro-5-phenyl-pyrrolopyrimidine in methanol was saturated with ammonia at 0°C, then heated in a sealed vessel at 140 °C for 20 hours. Concentration *in vacuo* gave an orange syrup which was purified by flash chromatography, eluting with methanol/ethyl acetate to give 50 mg of a white powder, mp 90-95 °C. Mass spectrum: [M+H] m/z 327. Analysis: $C_{23}H_{22}N_4O_3$·(1.0 HCl)(0.5 acetamide) found: C 55.48, H 5.88, N 16.20. $[a]_D^{25}$= -5.4 ° (c = 1.0 CH_3OH).

EXAMPLE 12: Synthesis of **N7-((1'R,2'S,3'R,4'S)-2',3'-dihydroxy-4'-amino-cyclopentyl)-4-chloro-5-iodo-pyrrolopyrimidine**: Dry hydrogen chloride gas

was bubbled through a suspension of 108 mg of N7-((1'R,2'S,3'R,4'S)-2',3'-dihydroxy-4'-(bis-t-butoxycarbonylamino)-cyclopentyl)-4-chloro-5-iodo-pyrrolo- pyrimidine in diethyl ether at 25 °C until saturated. The mixture was stirred at 25 °C for 4 hours, then concentrated *in vacuo*. The residue was dissolved in methanol and concentrated *in vacuo* to a powder. Mass spectrum: [M+H] m/z 395. A portion of the sample was further purified by reversed phase (C18) high pressure liquid chromatography, eluting with methanol/50 mM ammonium acetate to give a white powder, mp > 150 °C (decomp.). Analysis: $C_{11}H_{12}N_4O_2 \cdot ICl(0.4\ HCl)(1.1$ acetic acid) found: C 33.32, H 3.88, N 11.57. IR (KBr) 2300-3600, 1580, 1410 cm^{-1}.

EXAMPLE 13: Synthesis of **N7-((1'R,2'S,3'R,4'S)-2',3',4'-tri-acetoxycyclopentyl)-4,5-bis-phenylacetylenyl-pyrrolopyrimidine and N7-((1'R,2'S,3'R,4'S)-2',3',4'-triacetoxycyclopentyl)-4-chloro-5-phenyl-acetylenyl-pyrrolopyrimidine**: A solution of 207 mg of N7-((1'R,2'S,3'R,4'S)-2',3',4'-triacetoxycyclopentyl)-4-chloro-5-iodo-pyrrolo-pyrimidine, 28 mg of bis(triphenylphosphine)palladium(II)dichloride, 7.6 mg of copper(I) iodide, 121 mg of phenylacetylene, and 4 mL of triethylamine in acetonitrile was heated at 60 °C for six hours. Concentration *in vacuo* gave a syrup which was purified by flash chromatography, eluting with CH_2Cl_2/ethyl acetate to give 144 mg of N7-((1'R,2'S,3'R,4'S)-2',3',4'-triacetoxycyclopentyl)-4,5-bis-phenylacetylenyl-pyrrolopyrimidine as a white glass. Mass spectrum: [M+H] m/z 562. Analysis: $C_{33}H_{27}N_3O_6 \cdot (0.4$ ethyl acetate) found: C 69.50 H 4.93, N 7.08. $[a]_D^{25} = -34.35$ (c = 1.0, ethylacetate).

Also obtained was 40 mg of N7-((1'R,2'S,3'R,4'S)-2',3',4'-triacetoxy-cyclopentyl)-4-chloro-5-phenylacetylenyl-pyrrolopyrimidine as a white glass: Mass spectrum: [M+H] m/z 496.

EXAMPLE 14: Synthesis of **N7-((1'R,2'S,3'R,4'S)-2',3',4'-tri-acetoxycyclopentyl)-4,5-dichloro-pyrrolopyrimidine**: A mixture of 135 mg of N7-((1'R,2'S,3'R,4'S)-2',3',4'-triacetoxycyclopentyl)-4-chloro-pyrrolopyrimidine and 46 mg of N-chlorosuccinimide in CH_2Cl_2 was stirred under nitrogen at 25 °C for 72 hours, then another 300 mg of N-chlorosuccinimide was added. After stirring for another 5 days, the mixture was quenched by adding 15% sodium thiosulfate/saturated sodium monohydrogen phosphate solution, then poured into ethyl acetate and

washed with more 15% sodium thiosulfate/saturated sodium monohydrogen phosphate solution. The organic phase was dried ($MgSO_4$), and concentrated *in vacuo*. The resulting oil was purified by flash chromatography, eluting with ethyl acetate/dichloromethane, to give a white foam. Mass spectrum: [M+H] m/z 430. Analysis: $C_{17}H_{17}N_3O_6Cl_2$ found: C 47.58, H 4.08, N 9.50. $[a]_D^{25}$= +11.45 ° (c = 1.05, ethyl acetate).

EXAMPLE 15: Synthesis of **N7-((1'R,2'S,3'R,4'S)-2',3',4'-tri-hydroxycyclopentyl)-4-chloro-5-phenylacetylenyl-pyrrolopyrimidine**: A solution of 38 mg of N7-((1'R,2'S,3'R,4'S)-2',3',4'-triacetoxycyclopentyl)-4-chloro-5-phenylacetylenyl-pyrrolopyrimidine in methanol was cooled to 0 °C and saturated with ammonia. After stirring at 25 °C in a sealed flask for 24 hours, the solution was concentrated *in vacuo* to give a syrup which was purified by flash chromatography, eluting with methanol/ethyl acetate to give 32 mg of N7-((1'R,2'S,3'R,4'S)-2',3',4'-trihydroxycyclopentyl)-4-chloro-5-phenylacetylenyl-pyrrolopyrimidine as a white glass. Mass spectrum: [M+H] m/z 370. Analysis: $C_{19}H_{16}N_3O_3Cl$·(0.5 methanol) found: C 60.61, H 4.48, N 10.90. $[a]_D^{25}$= -73.96 ° (c = 0.34, methanol).

EXAMPLE 16: Synthesis of **N7-((1'R,2'S,3'R,4'S)-2',3',4'-tri-hydroxycyclopentyl)-4,5-dichloro-pyrrolopyrimidine**: A solution of 90 mg of N7-((1'R,2'S,3'R,4'S)-2',3',4'-triacetoxycyclopentyl)-4,5-dichloro-pyrrolopyrimidine in methanol was saturated with ammonia. After stirring at 25 °C in a sealed flask for 16 hours, the solution was concentrated *in vacuo* to give a syrup which was purified by flash chromatography, eluting with methanol/ethyl acetate to give 75 mg of N7-((1'R,2'S,3'R,4'S)-2',3',4'-trihydroxycyclopentyl)-4,5-dichloro-pyrrolopyrimidine as a white powder, mp 128-130 °C. Mass spectrum: [M+H] m/z 304. Analysis: $C_{11}H_{11}N_3O_3Cl_2$·(0.5 water) found: C 42.26, H 4.04, N 13.26. $[a]_D^{25}$= -38.93 ° (c = 0.45, methanol).

EXAMPLE 17: Synthesis of **N7-((1'R,2'S,3'R,4'S)-2',3',4'-tri-hydroxycyclopentyl)-4,5-bis-phenylacetylenyl-pyrrolopyrimidine**: A solution of 121 mg of N7-((1'R,2'S,3'R,4'S)-2',3',4'-triacetoxycyclopentyl)-4,5-bis-phenylacetylenyl-pyrrolopyrimidine in methanol was saturated with ammonia. After stirring at 25 °C in a sealed flask for 16 hours, the solution was concentrated *in vacuo* to give a syrup which was purified by flash

chromatography, eluting with methanol/ethyl acetate to give 75 mg of N7-((1'R,2'S,3'R,4'S)-2',3',4'-trihydroxycyclopentyl)-4,5-bis-phenylacetylenyl-pyrrolopyrimidine as a yellow powder. Mass spectrum: [M+H] m/z 436. Analysis: $C_{27}H_{21}N_3O_3$·(1.1 water) found: C 71.08, H 4.93, N 9.16. $[a]_D^{25}$= -81.73 ° (c = 0.32, methanol).

EXAMPLE 18: Synthesis of **N7-((1'R,2'S,3'R,4'S)-2',3',4'-tri-hydroxycyclopentyl)-4-amino-5-phenylacetylenyl-pyrrolopyrimidine**: A solution of 169 mg of N7-((1'R,2'S,3'R,4'S)-2',3',4'-trihydroxycyclopentyl)-4-chloro-5-iodo-pyrrolopyrimidine, 32 mg of bis(triphenylphosphine)-palladium(II)dichloride, 8.7 mg of copper(I) iodide, 145 mg of phenylacetylene, and 4.5 mL of triethylamine in 5 mL of DMF was heated at 69 °C for six hours. Concentration *in vacuo* gave a syrup which was dissolved in water and lyophilized. The spongy foam was purified by flash chromatography, eluting with methanol/ethyl acetate to give N7-((1'R,2'S,3'R,4'S)-2',3',4'-trihydroxy-cyclopentyl)-4-amino-5-phenyl-acetylenyl-pyrrolopyrimidine as a yellow glass. Mass spectrum: [M+H] m/z 351. The glass was dissolved in aqueous HCl, then dried *in vacuo* to constant weight: Analysis: $C_{19}H_{18}N_4O_3$·(4.0 HCl) found: C 46.07, H 4.09, N 11.67. $[a]_D^{25}$= -45.57 ° (c = 0.79, methanol).

EXAMPLE 19: Synthesis of **N7-((1'R,4'R)-trans-4'-acetoxy-2'-cyclopentenyl)-4-chloro-5-iodo-pyrrolopyrimidine**: A mixture of 2.08 g of 4-chloro-5-iodopyrrolopyrimdine 882 mg of (1R,4S)-cis-4-(hydroxy)-1-acetoxy-2-cyclopentene, 1.95 g of triphenylphosphine, and 1.2 g of diethylazodicarboxylate in 20 mL of tetrahydrofuran was stirred under nitrogen at 25 °C for 22 hours, then concentrated *in vacuo* to a white paste. The paste was suspended in boiling ethyl acetate, and after cooling, filtered and washed with ethyl acetate then dried *in vacuo* to give 1.46 g of a fine white powder, mp 204 °C (decomp.). Mass spectrum: [M+H] m/z 404. Analysis: ($C_{13}H_{11}N_3O_2ICl$) found: C 38.69, H 2.54, N 10.28. $[a]_D^{25}$= +183.65 ° (c = 0.69, CH_2Cl_2). IR (KBr pellet) 1730 cm^{-1}.

EXAMPLE 20: Synthesis of **N7-((1'R,4'R)-trans-4'-hydroxy-2'-cyclopentenyl)-4-chloro-5-iodo-pyrrolopyrimidine**: A suspension of 4.68 g of N7-((1'R,4'R)-trans-4'-acetoxy-2'-cyclopentenyl)-4-chloro-pyrrolopyrimidine in methanol was cooled to 0 °C in an ice water bath and saturated with NH_3 and stirred

under nitrogen at 25 °C for 40 hours, then concentrated *in vacuo* to a white solid. The solid was suspended in boiling methanol, and after cooling, filtered and washed with methanol then dried *in vacuo* to give 3.58 g of a fine white powder. Mass spectrum: [M+H] m/z 362. Analysis: ($C_{11}H_9N_3OICl$) found: C 36.60, H 2.50, N 11.82. IR (KBr pellet) 3100 cm^{-1}.

EXAMPLE 21: Synthesis of **N7-((1'R,4'S)-cis-4'-(bis-t-butoxy-carbonylamino)-2'-cyclopentenyl)-4-chloro-5-iodo-pyrrolopyrimidine**: To a mixture of 400 mg of N7-((1'R,4'R)-trans-4'-hydroxy-2'-cyclopentenyl)-4-chloro-5-iodo-pyrrolopyrimidine, 337 mg of di-t-butyl-imino dicarboxylate, 319 mg of di-t-butyl azodicarboxylate, and 363 mg of triphenylphosphine in a dry flask under nitrogen was added tetrahydrofuran. The reaction was stirred at 25 °C for 24 hours, then partitioned between ethyl acetate and water. The organic phase was dried ($MgSO_4$), concentrated *in vacuo*, and purified by flash chromatography, eluting with acetone/dichloromethane to give 464 mg of a white solid, mp 137-142 °C. Mass spectrum: [M+H] m/z 561. Analysis: ($C_{21}H_{26}N_4O_4ICl$. (0.21 di-t-butylamino dicarboxylate) found: C 45.09, H 4.90, N 10.97. IR (KBr pellet) 1740, 1705 cm^{-1}. $[a]_D^{25}$= +56.94 ° (c = 0.71, dichloromethane).

EXAMPLE 22: Synthesis of **N7-((1'R,2'S,3'R,4'S)-2',3'-dihydroxy-4'-(bis-t-butoxycarbonylamino)-cyclopentyl)-4-chloro-5-iodo-pyrrolo-pyrimidine**: To a mixture of 400 mg of N7-((1'R,4'S)-cis-4'-(bis-t-butoxy-carbonylamino)-2'-cyclopentenyl)-4-chloro-5-iodo-pyrrolopyrimidine, and 250 mg of N-morpholine-N-oxide in 1.5 mL of tetrahydrofuran at 0 °C was added 1.5 mL of a 2.5% solution of osmium tetroxide in t-butanol under nitrogen. The reaction was allowed to warm to 25 °C and stirred 2.5 hours, then poured into ethyl acetate and washed with a mixture of 10% sodium thiosulfate and sodium phosphate buffer (pH 7). The organic phase was dried (Na_2SO_4), concentrated *in vacuo*, and purified by flash chromatography, eluting with acetone/hexane to give 348 mg of a white solid. Mass spectrum: [M+H] m/z 595. Analysis: ($C_{21}H_{28}N_4O_6ICl$) found: C 42.57, H 4.74, N 9.24. $[a]_D^{25}$= -1.1 ° (c = 0.46, ethyl acetate). IR (KBr) 3000-3650, 1740, 1700 cm^{-1}.

EXAMPLE 23: Synthesis of **N7-((1'R,2'S,3'R,4'S)-2',3'-dihydroxy-4'-amino-cyclopentyl)-4-amino-5-iodo-pyrrolopyrimidine**: Dry hydrogen chloride gas

was bubbled through a suspension of 108 mg of N7-((1'R,2'S,3'R,4'S)-2',3'-dihydroxy-4'-(t-butoxycarbonylamino)-cyclopentyl)-4-amino-5-iodo-pyrrolopyrimidine in diethyl ether at 25 °C until saturated. The mixture was stirred at 25 °C for 4 hours, then concentrated *in vacuo* . The residue was dissolved in methanol and concentrated *in vacuo* to a powder. Mass spectrum: [M+H] m/z 376. Analysis: ($C_{11}H_{14}N_5O_2I$) found: C 29.78, H 3.62, N 15.35. A portion of the sample was further purified by reversed phase (C18) high pressure liquid chromatography, eluting with methanol/50 mM ammonium acetate to give a white powder: IR (KBr) 2000-3600, 1630, 1405 cm^{-1}.

EXAMPLE 24: Synthesis of **N7-((1'R,2'S,3'R,4'S)-2',3'-dihydroxy-4'-(trifluoroacetyl)amino-cyclopentyl)-4-chloro-5-iodo-pyrrolo-pyrimidine** and **N7-((1'R,2'S,3'R,4'S)-2',3'-dihydroxy-4'-(trifluoro-acetyl)amino-cyclopentyl)-4-hydroxy-5-iodo-pyrrolopyrimidine**: To a solution of 136 mg of N7-((1'R,2'S,3'R,4'S)-2',3'-dihydroxy-4'-(bis-t-butoxycarbonylamino)-cyclopentyl)-4-chloro-5-iodo-pyrrolopyrimidine, in 5 mL of dioxane was added 5 mL of 4-M aqueous hydrochloric acid at 25 °C. The reaction was stirred for 24 hours, after which 10 mL of water was added, and the mixture lyophilized. The resulting yellow powder was dissolved in methanol, and 0.28 mL of ethyl trifluoroacetate and 0.32 mL of triethylamine was added. After one hour, the reaction was poured into sodium phosphate buffer (pH 7) and extracted with ethyl acetate. The organic layer was washed with water, and saturated sodium chloride, dried over Na_2SO_4, and concentrated *in vacuo*. The residue was purified by flash chromatography, eluting with methanol/ethyl acetate/dichloromethane, to give N7-((1'R,2'S,3'R,4'S)-2',3'-dihydroxy-4'-(trifluoroacetyl)amino-cyclopentyl)-4-chloro-5-iodo-pyrrolopyrimidine as a clear oil: Mass spectrum: [M+H] m/z 491. ^1H NMR (300 MHz, DMSO): ∂ 1.91 (ddd, 1H), 2.63 (ddd, 1H), 3.93 (m, 1H), 4.12 (m, 1H), 4.30 (m, 1H), 5.07 (q, 1H), 5.15 (d, 1H), 5.24 (d, 1H), 8.13 (s, 1H), 8.63 (s, 1H), 9.54 (d, 1H).

Also isolated was N7-((1'R,2'S,3'R,4'S)-2',3'-dihydroxy-4'-(trifluoro-acetyl)amino-cyclopentyl)-4-hydroxy-5-iodo-pyrrolopyrimidine as a clear glass: Mass spectrum: [M+H] m/z 473. ^1H NMR (300 MHz, DMSO): 1.80 (ddd, 1H), 2.55 (ddd, 1H), 3.87 (m, 1H), 4.09 (m, 1H), 4.18 (m, 1H), 4.88 (q, 1H), 5.13 (d, 1H), 5.22 (d, 1H), 7.48 (s, 1H), 7.89 (d, 1H), 9.58 (d, 1H), 12.01 (d, 1H).

EXAMPLE 25: Synthesis of **N7-((1'R,2'S,3'R,4'S)-2',3'-dihydroxy-4'-(t-butoxycarbonylamino)-cyclopentyl)-4-amino-5-iodo-pyrrolo-pyrimidine**: A suspension of 1.2 g of N7-((1'R,2'S,3'R,4'S)-2',3'-dihydroxy-4'-(bis-t-butoxy-carbonylamino)-cyclopentyl)-4-chloro-5-iodo-pyrrolopyrimidine in 20 mL of methanol was cooled to -50 °C and ammonia was bubbled through the solution until about 20 mL of ammonia had been condensed. The solution was heated at 129 °C in a sealed vessel for 14 hours, then cooled, and the ammonia allowed to evaporate. The methanol was removed by concentration *in vacuo* and the residue purified by flash chromatography, eluting with methanol/dichloromethane to give 777 mg of a white solid, mp 170-171 °C. Mass spectrum: [M+H] m/z 476. Analysis: ($C_{16}H_{22}N_5O_4I$) found: C 40.24, H 4.58, N 14.51. $[a]_D^{25}$= -28.51° (c = 0.20, dichloromethane). IR (KBr) 3470, 3300, 3200, 1670, 1630 cm^{-1}.

EXAMPLE 26: Synthesis of **N7-((1'R,2'S,3'R,4'S)-2',3'-O-(2"-oxo-1",3"-dioxalyl)-4'-amino-cyclopentyl)-4-chloro-5-iodo-pyrrolo-pyrimidine**: To a solution of 208 mg N7-((1'R,2'S,3'R,4'S)-2',3'-dihydroxy-4'-(bis-t-butoxycarbonylamino)-cyclopentyl)-4-chloro-5-iodo-pyrrolopyrimidine in 5 mL of DMF was added 57 mg of carbonyl diimidazole. After 5 hours at 25 °C, an additional 57 mg of carbonyl diimidazole was added. After 24 hours, the reaction was poured into ethyl acetate/hexane and washed with water, and saturated sodium chloride, dried over Na_2SO_4, and concentrated *in vacuo*, and passed over a short flash column, eluting with ethyl acetate/dichloromethane. Concentration *in vacuo* of product-containing fractions gave N7-((1'R,2'S,3'R,4'S)-2',3'-O-(2"-oxo-1",3"-dioxalyl)-4'-(bis-t-butoxycarbonylamino)-cyclopentyl)-4-chloro-5-iodo-pyrrolopyrimidine. A solution of 217 mg of N7-((1'R,2'S,3'R,4'S)-2',3'-O-(2"-oxo-1",3"-dioxalyl)-4'-(bis-t-butoxycarbonylamino)-cyclopentyl)-4-chloro-5-iodo-pyrrolopyrimidine in ether was saturated with dry hydrogen chloride. After 2 hours, the reaction was concentrated *in vacuo* to a yellow paste of N7-((1'R,2'S,3'R,4'S)-2',3'-O-(2"-oxo-1",3"-dioxalyl)-4'-amino-cyclopentyl)-4-chloro-5-iodo-pyrrolopyrimidine. Mass spectrum: [M+H] m/z 421. ^1H NMR (300 MHz, CD_3OD): ∂ 2.65-2.80 (m, 2H), 4.09 (ddd, 1H), 5.36 (dd, 1H), 5.44 (ddd, 1H), 5.68 (dd, 1H), 7.91 (s, 1H), 8.62 (s, 1H).

EXAMPLE 27: Synthesis of **N7-((1'R,2'S,3'R,4'S)-2',3'-dihydroxy-4'-(acetyl)amino-cyclopentyl)-4-chloro-5-iodo-pyrrolopyrimidine**: To a solution of 154 mg of N7-((1'R,2'S,3'R,4'S)-2',3'-diacetoxy-4'-acetamido-2'-cyclopentyl)-4-chloro-5-iodo-pyrrolopyrimidine in methanol was saturated with ammonia. After stirring for 3.5 hours at 25 °C, the reaction was concentrated *in vacuo* and the white powder recrystallized from ethanol/ethyl acetate to give a white powder, mp >245 °C (dec.) Mass spectrum: [M+H] m/z 437. Analysis: ($C_{13}H_{14}N_4O_3ICl$) found: C 35.79, H 3.32, N 12.60. IR (KBr) 2980-3620, 1645 cm^{-1}. $[a]_D^{25}$= -17.42 ° (c=0.31, methanol).

EXAMPLE 28: Synthesis of **N7-((1'R,2'S,3'R,4'S)-2',3'-diacetoxy-4'-(acetyl)amino-cyclopentyl)-4-chloro-5-iodo-pyrrolopyrimidine**: To a solution of 114 mg of N7-((1'R,2'S,3'R,4'S)-2',3'-dihydroxy-4'-amino-cyclopentyl)-4-chloro-5-iodo-pyrrolopyrimidine in pyridine at 25 °C was added 147 mg of acetic anhydride. After stirring for three hours another 108 mg of acetic anhydride and 10 mg of DMAP (4-dimethylamino pyridine) was added. After a further 40 minutes, the reaction was quenched with 0.5 mL of water and poured into an ethyl acetate/dichloromethane mixture and washed with saturated sodium bicarbonate. The organic layer was dried over $MgSO_4$ and concentrated *in vacuo* to a syrup, which was purified by flash chromatography, eluting with methanol/dichloromethane, followed by another flash chromatography, eluting with acetonitrile/dichloromethane to give a clear glass. Mass spectrum: [M+H] m/z 521. Analysis: ($C_{17}H_{18}N_4O_5ICl$) found: C 39.46, H 3.59, N 10.48. IR (KBr) 3400, 3280, 1740, 1660 cm^{-1}. $[a]_D^{25}$= -4.95 ° (c=0.93, methanol)

EXAMPLE 29: Synthesis of **N7-((1'R,2'S,3'R,4'S)-2',3'-dihydroxy-4'-(acetyl)amino-cyclopentyl)-4-amino-5-iodo-pyrrolopyrimidine**: Ammonia was bubbled through a solution of 30 mg of N7-((1'R,2'S,3'R,4'S)-2',3'-diacetoxy-4'-(acetyl)amino-cyclopentyl)-4-amino-5-iodo-pyrrolopyrimidine in 4 mL of methanol for 20 seconds. After 12 hours, thin layer chromatography revealed that a single product was present, and the reaction was concentrated *in vacuo*, washed with water, and dried *in vacuo* . Mass spectrum: [M+H] m/z 418. $[a]_D^{25}$= -36.21 ° (c = 1.0, 3:7 pyridine:methanol).

EXAMPLE 30: Synthesis of **N7-((1'R,2'S,3'R,4'S)-2',3'-O-(2"-oxo-1",3"-dioxalyl)-4'-(acetyl)amino-cyclopentyl)-4-chloro-5-iodo-pyrrolopyrimidine and N7-((1'R,2'S,3'R,4'S)-2',3'-O-(2"-oxo-1",3"-dioxalyl)-4'-(acetyl)-amino-cyclopentyl)-4-hydroxy-5-iodo-pyrrolopyrimidine**: To a solution of 72 mg of N7-((1'R,2'S,3'R,4'S)-2',3'-O-(2"-oxo-1",3"-dioxalyl)-4'-amino-cyclopentyl)-4-chloro-5-iodo-pyrrolopyrimidine in 2.5 mL of pyridine at 0 °C was added 17.5 µL of acetic anhydride. After 7 hours at 0 °C, the reaction was allowed to warm to 25 °C, and an additional 2.5 µL of acetic anhydride was added. After 24 hours, the reaction was concentrated *in vacuo*, and the residue purified by flash chromatography, eluting with methanol/dichloromethane. Concentration *in vacuo* of product-containing fractions gave N7-((1'R,2'S,3'R,4'S)-2',3'-O-(2"-oxo-1",3"-dioxalyl)-4'-(acetyl)amino-cyclopentyl)-4-chloro-5-iodo-pyrrolopyrimidine. Mass spectrum: [M+H] m/z 463. $[a]_D^{25}$= -6.94 °(c = 1.0, 3:7 pyridine/methanol).

Also isolated was N7-((1'R,2'S,3'R,4'S)-2',3'-O-(2"-oxo-1",3"-dioxalyl)-4'-(acetyl)amino-cyclopentyl)-4-hydroxy-5-iodo-pyrrolopyrimidine. Mass spectrum: [M+H] = 445. ^{1}H NMR (300 MHz, CD_3SOCD_3): ∂ 1.87 (s, 3H), 2.20 (m, 1H), 2.36 (m, 1H), 4.40 (m, 1H), 5.02 (dd, 1H), 5.29 (m, 1H), 5.38 (dd, 1H), 7.48 (s, 1H), 7.96 (s, 1H), 8.31 (d, 1H), 12.11 (s, 1H).

EXAMPLE 31: Synthesis of **N7-((1'R,2'S,3'R,4'S)-2',3',4'-tri-hydroxycyclopentyl)-4-amino-5-((2-phenyl)ethyl)-pyrrolopyrimidine**: A solution of 22 mg of N7-((1'R,2'S,3'R,4'S)-2',3',4'-trihydroxycyclopentyl)-4-amino-5-phenylacetylenyl-pyrrolopyrimidine and 20 mg of 10% palladium on carbon in methanol was stirred under an atmosphere of hydrogen for two weeks. The mixture was filtered, concentrated *in vacuo*, and purified by flash chromatography, eluting with methanol/ethyl acetate to give 14 mg of N7-((1'R,2'S,3'R,4'S)-2',3',4'-trihydroxycyclopentyl)-4-amino-5-((2-phenyl)-ethyl)-pyrrolopyrimidine as a white microcrystalline powder. Mass spectrum: [M+H] m/z 355. $[a]_D^{25}$= -25.97 ° (c = 0.33, methanol).

EXAMPLE 32: Synthesis of **N7-((1'R,2'S,3'R,4'S)-2',3'-dihydroxy-4'-(methyl)amino-cyclopentyl)-4-chloro-5-methyl-pyrrolopyrimidine**: A mixture of 320 mg of N7-((1'R,2'S,3'R,4'S)-2',3'-dihydroxy-4'-(bis-t-butoxycarbonylamino)-cyclopentyl)-4-chloro-5-iodo-pyrrolopyrimidine, 261 mg of imidazole, and 387 mg of t-butyldimethylsilyl chloride in

dimethylformamide was stirred at 25 °C for 24 hours, then poured into 65 mL of ethyl acetate and washed with sodium phosphate buffer (pH 7), water, then dried (Na_2SO_4), and concentrated *in vacuo* to give a clear oil. This was purified by flash chromatography, eluting with acetone/hexane to give 464 mg of N7((1'R,2'S,3'R,4'S)-2',3'-bis(t-butyldimethylsilyloxy)-4'-(bis-t-butoxycarbonylamino)-2'-cyclopentyl)-4-chloro-5-iodo-pyrrolopyrimidine.

A solution of 325 mg of N7-((1'R,2'S,3'R,4'S)-2',3'-bis(t-butyl-dimethylsilyloxy)-4'-(bis-t-butoxycarbonylamino)-cyclopentyl)-4-chloro-5-iodo-pyrrolopyrimidine in diethyl ether was cooled to -78 °C under nitrogen, and 0.49 mL of a 1.7 M solution of t-butyl lithium in pentane was added. After stirring at -78 °C for 20 minutes, 1.5 mL of HMPA (hexamethyl-phosphoric triamide), and 281 mg of iodomethane was added. This was stirred at -78 °C for two hours, then allowed to warm to -25 °C over 2 hours. The reaction was poured into ethyl acetate and washed with water, and dried over $MgSO_4$. The organic phase was concentrated *in vacuo* to a syrup, which was purified by flash chromatography, eluting with ethyl acetate/dichloromethane to give 135 mg of an oil, which was further purified by flash chromatography, eluting with diethyl ether/dichloromethane to give 43 mg of N7-((1'R,2'S,3'R,4'S)-2',3'-bis(t-butyldimethylsilyloxy)-4'-(((t-butoxy-carbonyl)methyl)amino)-cyclopentyl)-4-chloro-5-methyl-pyrrolopyrimidine as a white oil. Mass spectrum, [M+H] *m/z* 625.

To a solution of 43 mg of N7-((1'R,2'S,3'R,4'S)-2',3'-bis(t-butyldimethylsilyloxy)-4'-(((t-butoxycarbonyl)methyl)amino)-cyclopentyl)-4-chloro-5-methyl-pyrrolopyrimidine in THF was added 0.6 mL of a 1 M solution of TBAF (tetra-n-butylammonium fluoride) in THF. After 2 hours, the reaction was poured into a dichloromethane/ethyl acetate mixture, and washed with water, then dried (Na_2SO_4), and concentrated *in vacuo* to a clear glass. This was purified by flash chromatography, eluting with methanol/ethyl acetate to give 25 mg of N7-((1'R,2'S,3'R,4'S)-2',3'-dihydroxy-4'-((t-butoxycarbonyl)methylamino)-cyclopentyl)-4-chloro-5-methyl-pyrrolopyrimidine.

24 mg of N7-((1'R,2'S,3'R,4'S)-2',3'-dihydroxy-4'-(((t-butoxy-carbonyl)methyl)amino)-cyclopentyl)-4-chloro-5-methyl-pyrrolopyrimidine was dissolved in 1.9 mL of TFA (trifluoroacetic acid) and stirred at 25 °C for 90 minutes, then concentrated *in vacuo* . A mixture of chloroform/methanol was added and then removed by evaporation several times to remove excess

TFA (trifluoroacetic acid). The residue was purified by flash chromatography, eluting with methanol/acetic acid to give 31 mg of N7-((1'R,2'S,3'R,4'S)-2',3'-dihydroxy-4'-(methyl)amino-cyclopentyl)-4-chloro-5-methyl-pyrrolopyrimidine as a clear glass. Mass spectrum: [M+H] *m/z* 297. Analysis ($C_{13}H_{17}N_4O_2Cl$. (2.0 CF_3CO_2H)·(0.1 ethyl acetate)· (0.8 methanol)) found: C 39.09, H 4.15, N 10.02. $[a]_D^{25}$= -11.24 (c=0.35, methanol), IR (neat) 2800-3450, 1670 cm^{-1}.

EXAMPLE 33: Synthesis of **N7-((1'R,2'S,3'R,4'S)-2',3'-dihydroxy-4'-(methoxycarbonyl)amino-cyclopentyl)-4-chloro-5-iodo-pyrrolo-pyrimidine**: To a solution of 78 mg of N7-((1'R,2'S,3'R,4'S)-2',3'-dihydroxy-4'-amino-cyclopentyl)-4-chloro-5-iodo-pyrrolopyrimidine in pyridine was added 25 µL of triethylamine. The reaction was cooled to -30 °C, and 20 µL of methyl chloroformate was added. A solid formed which dissolved on warming to -5 °C. After 2 hours, the reaction was allowed to warm to 25 °C, and after 3 days, concentrated *in vacuo*. The residue was dissolved in methanol and saturated with ammonia. After 24 hours, the reaction was concentrated *in vacuo*, and the residue purified by flash chromatography, eluting with methanol/ethyl acetate/dichloromethane. Mass spectrum: [M+H] m/z 453. IR (neat) 3050-3550, 1710, 1580, 1450 cm^{-1}.

EXAMPLE 34: Synthesis of **N7-((1'R,2'S,3'R,4'S)-2',3'-dihydroxy-4'-(3''-nicotinyl)amino-cyclopentyl)-4-chloro-5-iodo-pyrrolopyrimidine**: To a solution of 78 mg of N7-((1'R,2'S,3'R,4'S)-2',3'-dihydroxy-4'-amino-cyclopentyl)-4-chloro-5-iodo-pyrrolopyrimidine and 50 µL of triethylamine in 2 mL of pyridine at 0 °C was added 32 mg of nicotinyl chloride hydrochloride. After 10 minutes the reaction was allowed to warm to 25 °C and stirred for 7 days. After concentration *in vacuo*, the residue was taken up in toluene, whereupon a precipitate was produced. This was collected and triturated successively from water, methanol, and ethyl acetate, and dried *in vacuo* to give the title product. Mass spectrum: [M+H] m/z 500. IR (neat) 3050-3550, 1660, 1565, 1170 cm^{-1}.

EXAMPLE 35: Synthesis of **N7-((1'R,2'S,3'R,4'S)-2',3'-diacetoxy-4'-(acetyl)amino-cyclopentyl)-4-amino-5-iodo-pyrrolopyrimidine**: To a solution of 75 mg of N7-((1'R,2'S,3'R,4'S)-2',3'-dihydroxy-4'-amino-cyclopentyl)-4-

amino-5-iodo-pyrrolopyrimidine in 4 mL of pyridine was added 28 µL of triethylamine at 0 °C. Acetic anhydride (75 µL) was added dropwise, and after one hour, the reaction was concentrated *in vacuo* and redissolved in 4 mL of pyridine, and 21 µL of acetic anhydride was added. After 24 hours, 28 µL of triethylamine was added, and after 24 hours, another 21 µL of acetic anhydride was added. The solution was concentrated *in vacuo* and residual solvent removed by azeotropic evaporation with toluene. Recrystallization from ethanol/ethyl acetate gave a white solid. Mass spectrum: [M+H] m/z 502. ^{1}H NMR (300 MHz, CD_3SOCD_3) ∂ 1.87 (s, 3H), 1.90 (s, 3H), 1.98 (ddd, 1H), 2.07 (s, 3H), 2.57 (ddd, 1H), 4.22 (ddd, 1H), 5.09 (q, 1H), 5.20 (dd, 1H), 5.60 (dd, 1H), 6.65 (bs, 1H), 7.60 (s, 1H), 8.12 (s, 1H), 8.35 (d, 1H).

EXAMPLE 36: Synthesis of **N7-((1'R,2'S,3'R,4'S)-2',3'-dihydroxy-4'-(dimethyl)amino-cyclopentyl)-4-chloro-5-iodo-pyrrolopyrimidine**: To a solution of 72 mg of N7-((1'R,2'S,3'R,4'S)-2',3'-dihydroxy-4'-amino-cyclopentyl)-4-chloro-5-iodo-pyrrolopyrimidine in 0.9 mL of 50 mM sodium phosphate buffer at pH 4.6 was added 0.12 mL of 37% formaldehyde and 30 mg of sodium cyanoborohydride. Acetic acid was added to adjust the pH to 4.5, and after stirring for 90 minutes at 25 °C, the reaction was made basic with KOH and extracted with ethyl acetate. The organic phase was washed with saturated sodium chloride, dried, and concentrated *in vacuo*. The residue was dissolved in 1 M HCl and lyophilized to a glass, which was purified by flash chromatography, eluting with methanol/ethyl acetate, to give a tan solid. The residue was further purified by high pressure liquid C18 reversed phase chromatography, eluting with methanol/50 mM ammonium acetate. Concentration gave a hygroscopic white glass. Mass spectrum: [M+H] m/z 423. Analysis: ($C_{13}H_{16}N_4O_2ICl$(1.2 acetic acid)(0.1 hydrochloric acid)(1.0 water) found: C 35.83, H 4.47, N 10.82. IR (KBr) 2800-3650 cm-1, 1575, 1530, 1500.

EXAMPLE 37 Synthesis of **N1-((1'R,4'R)-trans-4'-acetoxy-2'-cyclopentenyl)-4-amino-3-bromo-pyrazolopyrimdine**: To a suspension of 3 mMoles of 4-amino-3-bromopyrazolopyrimidine, 3 mMole of (1R,4S)-cis-4-(hydroxy)-1-acetoxy-2-cyclopentene, and 3 mMole of triphenylphosphine in tetrahydrofuran is added 3 mMole of diethylazodicarboxylate. The reaction is stirred under nitrogen at 25 °C for 48 hours, then poured into ethyl acetate and washed successively with saturated sodium bicarbonate, saturated

potassium bisulfate, and saturated sodium chloride solution. The organic layer is dried over $MgSO_4$, and concentrated *in vacuo* to afford the title compound.

EXAMPLE 38: Synthesis of **N1-((1'R,4'R)-trans-4'-hydroxy-2'-cyclo-pentenyl)-4-amino-3-bromopyrazolopyrimdine**: A suspension of 1 mMole of N1-((1'R,4'R)-trans-4'-acetoxy-2'-cyclopentenyl)-4-amino-3-bromo-pyrazolopyrimdine in methanol is saturated with ammonia and stirred in a sealed vessel for 48 hours. Concentration *in vacuo* affords the title product.

EXAMPLE 39: Synthesis of **N1-((1'R,4'S)-cis-4'-phthalimido-2'-cyclo-pentenyl)-4-amino-3-bromo-pyrazolopyrimdine**: To a mixture of 1 mMole of N7-((1'R,4'R)-trans-4'-hydroxy-2'-cyclopentenyl)-4-amino-3-bromopyrazolopyrimdine, 1 mMole of phthalimide, 1 mMole of diethyl-azodicarboxylate, and 1 mMole of triphenylphosphine in a dry flask under nitrogen is added tetrahydrofuran. The reaction is stirred at 25 °C for 24 hours, then concentrated *in vacuo*, and purified by flash chromatography.

EXAMPLE 40: Synthesis of **N1-((1'R,2'S,3'R,4'S)-2',3'-dihydroxy-4'-phthalimido-cyclopentyl)-4-amino-3-bromo-pyrazolopyrimdine**: To a solution of 1 mMole of N1-((1'R,4'S)-cis-4'-phthalimido-2'-cyclo-pentenyl)-4-amino-3-bromo-pyrazolopyrimdine in t-butanol/tetrahydrofuran at 10°C is added 3 mMole of N-methylmorpholine-N-oxide and 0.2 mMole of solid osmium tetroxide. The mixture is allowed to warm to 25 °C, stirred for 12 hours, then poured into dichloromethane and washed with a mixture of 10% sodium thiosulfate and sodium phosphate buffer (pH 7). The organic phase is dried (Na_2SO_4), concentrated *in vacuo*, and purified by flash chromatography to give the title compound.

EXAMPLE 41: Synthesis of **N1-((1'R,2'S,3'R,4'S)-2',3'-dihydroxy-4'-amino-cyclopentyl)-4-amino-3-bromo-pyrazolopyrimdine**: To a suspension of 1 mMole of N1-((1'R,2'S,3'R,4'S)-2',3'-dihydroxy-4'-phthalimido-cyclopentyl)-4-amino--bromo-p3yrazolopyrimdine in ethanol is added 5 mMole of hydrazine hydrate. The reaction is heated at reflux for 12 hours, cooled, and concentrated *in vacuo* . The residue is purified by flash chromatography to give the title compound.

EXAMPLE 42: Synthesis of **N7-((1'R,2'S,3'R,4'S)-2',3'-dihydroxy-4'-(3"-chloro-pyridazin-6"-yl)amino-cyclopentyl)-4-amino-5-iodo-pyrrolo-pyrimidine**: A suspension of 174 mg of N7-((1'R,2'S,3'R,4'S)-2',3'-dihydroxy-4'-amino-cyclopentyl)-4-amino-5-iodo-pyrrolopyrimidine, 170 mg of 3,6-dichloropyridazine, and 385 mg of di-isopropylethylamine in 3.5 mL of DMSO was heated at 90 °C for 33 hours, then was cooled, and the reaction mixture poured into water and extracted with chloroform/ethyl acetate. The organic layer was dried over sodium sulfate, and the residue was purified by flash chromatography, using methanol/dichloromethane as eluant to give the product as a white powder, mp 190-194 °C. Mass spectrum $[M+H]^+$ m/z 488. IR (neat) 3450, 3100-3400, 1625, 1600, 1590 cm^{-1}.

EXAMPLE 43: Synthesis of **N7-((1'R,2'S,3'R,4'S)-2',3'-dihydroxy-4'-(3"-dimethylamino-pyridazin-6"-yl)amino-cyclopentyl)-4-amino-5-iodo-pyrrolopyrimidine**: A suspension of 1 mMole of N7-((1'R,2'S,3'R,4'S)-2',3'-dihydroxy-4'-(3"-chloro-pyridazinyl-6"-yl))amino-cyclopentyl)-4-amino-5-iodo-pyrrolo-pyrimidine in dimethylamine/ethanol is heated in a sealed tube at 130 °C for six hours, then cooled, and the reaction concentrated *in vacuo*. The residue is purified by flash chromatography to give the product.

EXAMPLE 44: Synthesis of **N7-((1'R,2'S,3'R,4'S)-2',3'-dihydroxy-4'-(pyridin-2"-yl)amino-cyclopentyl)-4-amino-5-iodo-pyrrolopyrimidine**: A suspension of 1 mMole of N7-((1'R,2'S,3'R,4'S)-2',3'-dihydroxy-4'-amino-cyclopentyl)-4-amino-5-iodo-pyrrolopyrimidine and 20 mMole of 2-fluoropyridine in triethylamine/ethanol is heated in a sealed tube at 130 °C for six hours, then cooled, and the reaction concentrated *in vacuo*. The residue is purified by flash chromatography to give the product.

EXAMPLE 45: Synthesis of **N7-((1'R,2'S,3'R,4'S)-2',3'-dihydroxy-4'-amino-cyclopentyl)-4-amino-5-phenyl-pyrrolopyrimidine:** A mixture of 1 mMole of N7-((1'R,2'S,3'R,4'S)-2',3'-dihydroxy-4'-(t-butoxycarbonyl)amino-cyclopentyl)-4-amino-5-iodo-pyrrolopyrimidine, 1.2 mMole of phenyl-trimethylstannane, and 0.05 mMole of tetrakis-triphenylphosphine palladium (0) in DMF is heated at 70 °C for 12 hours, then cooled, and concentrated *in vacuo* to a syrup. The residue is purified by flash chromatography to give N7-

((1'R,2'S,3'R,4'S)-2',3'-dihydroxy-4'-(t-butoxycarbonyl)amino-cyclopentyl)-4-amino-5-phenyl-pyrrolopyrimidine. This is dissolved in trifluoroacetic acid and after stirring at 25 °C for one hour, concentrated *in vacuo* to yield the title compound, N7-((1'R,2'S,3'R,4'S)-2',3'-dihydroxy-4'-amino-cyclopentyl)-4-amino-5-phenyl-pyrrolopyrimidine.

EXAMPLE 46: Synthesis of **N7-((1'R,2'S,3'R,4'S)-2',3'-dihydroxy-4'-amino-cyclopentyl)-4-amino-5-methyl-pyrrolopyrimidine:** A mixture of 1 mMole of N7-((1'R,2'S,3'R,4'S)-2',3'-dihydroxy-4'-(t-butoxycarbonyl)amino-cyclopentyl)-4-amino-5-iodo-pyrrolopyrimidine, 1.2 mMole of tetramethylstannane ($Sn(CH_3)_4$), and 0.05 mMole of tetrakis-triphenylphosphine palladium (0) in DMF is heated at 70 °C for 12 hours, then cooled, and concentrated *in vacuo* to a dark syrup. The residue is purified by flash chromatography to give N7-((1'R,2'S,3'R,4'S)-2',3'-dihydroxy-4'-(t-butoxycarbonyl)amino-cyclopentyl)-4-amino-5-methyl-pyrrolopyrimidine. This is dissolved in trifluoroacetic acid and after stirring at 25 °C for one hour, concentrated *in vacuo* to yield the title compound, N7-((1'R,2'S,3'R,4'S)-2',3'-dihydroxy-4'-amino-cyclopentyl)-4-amino-5-methyl-pyrrolopyrimidine.

EXAMPLE 47: Synthesis of **N7-((1'R,2'S,3'R,4'S)-2',3'-dihydroxy-4'-amino-cyclopentyl)-4-amino-5-(pyridin-3-yl)pyrrolopyrimidine:** A mixture of 1 mMole of N7-((1'R,2'S,3'R,4'S)-2',3'-dihydroxy-4'-(t-butoxycarbonyl)amino-cyclopentyl)-4-amino-5-iodo-pyrrolopyrimidine, 1.2 mMole of 3-(tributylstannyl)-pyridine, and 0.05 mMole of tetrakis-triphenylphosphine palladium (0) in DMF is heated at 70 °C for 12 hours, then cooled, and concentrated *in vacuo* to a dark syrup. The residue is purified by flash chromatography to give N7-((1'R,2'S,3'R,4'S)-2',3'-dihydroxy-4'-(t-butoxycarbonyl)amino-cyclopentyl)-4-amino-5-(pyridin-3-yl)-pyrrolopyrimidine. This is dissolved in trifluoroacetic acid and after stirring at 25 °C for one hour, concentrated *in vacuo* to yield the title compound, N7-((1'R,2'S,3'R,4'S)-2',3'-dihydroxy-4'-amino-cyclopentyl)-4-amino-5-(pyridin-3-yl)-pyrrolopyrimidine.

EXAMPLE 48: Synthesis of **N7-((1'R,2'S,3'R,4'S)-2',3'-dihydroxy-4'-(1"-methylimidazole-4"-sulfonyl)amino-cyclopentyl)-4-amino-5-iodo-pyrrolopyrimidine:** To a suspension of 1 mMole of N7-((1'R,2'S,3'R,4'S)-2',3'-

dihydroxy-4'-amino-cyclopentyl)-4-amino-5-iodo-pyrrolopyrimidine in triethylamine/pyridine at 0 °C is added 1 mMole of 1-methylimidazole-4-sulphonyl chloride (Maybridge Chemical Co.). The reaction is allowed to warm to 25 °C, and stirred for 2 hours, concentrated *in vacuo*. The residue is purified by flash chromatography to give the product.

EXAMPLE 49: Synthesis of **N7-((1'R,4'S)-4'-(pyridin-3''-yl)oxy-cyclopentenyl)-4-chloro-5-iodo-pyrrolopyrimidine**: To a mixture of 140 mg of N7-((1'R,4'R)-trans-4'-hydroxy-2'-cyclopentenyl)-4-chloro-5-iodo-pyrrolopyrimidine, 55 mg of 3-hydroxypyridine, 142 mg of triphenylphosphine, and 125 mg of di-t-butyl azodicarboxylate in dichloromethane was stirred for two days, then poured into ethyl acetate and extracted with hydrochloric acid. The aqueous phase was then made basic with aqueous ammonia and extracted with dichloromethane. The organic phase was dried with sodium sulfate, concentrated *in vacuo*, and purified by flash chromatography, eluting with acetone/dichloromethane to give the product as a white powder, mp 163-165 °C. Analysis ($C_{16}H_{12}N_4OICl$)(0.1 acetone) found: C 44.42, H 2.57, N 12.53. IR (neat) 1570, 1440 cm^{-1}.

EXAMPLE 50: Synthesis of **N7-((1'R,4'S)-cis-4'-(acetylmercapto)-2'-cyclopentenyl-4-chloro-5-iodo-pyrrolopyrimidine**: To a mixture of 1 mMole of N7-((1'R,4'R)-trans-4'-hydroxy-2'-cyclopentyl)-4-chloro-pyrrolopyrimidine, 1 mMole of thiolacetic acid, 1 mMole of di-t-butyl azodicarboxylate, and 1 mMole of triphenylphosphine is added dichloromethane in a dry flask under nitrogen. The reaction is stirred at 25 °C for 48 hours, then concentrated *in vacuo*, and purified by flash chromatography to give the title compound.

EXAMPLE 51: Synthesis of **N7-((1'R,2'S,3'S,4'S)-2',3'-dihydroxy-4'-mercapto-cyclopentyl)-4-chloro-5-iodo-pyrrolopyrimidine**: To a solution of 1 mMole of N7-((1'R,4'S)-cis-4'-(acetylmercapto)-2'-cyclopentenyl)-4-chloro-5-iodo-pyrrolopyrimidine in t-butanol is added 1 mMole of solid osmium tetroxide. After stirring at 25 °C for 12 hours, hydrogen sulfide gas is bubbled through the reaction, followed by addition of 2 M ammonia in methanol. After one hour, the reaction is concentrated *in vacuo* and the residue purified by flash chromatography to give the title compound.

EXAMPLE 52: Synthesis of **N7-((1'R,4'S)-2',3'-dihydroxy-4'-(3''-picolylmercapto)-cyclopentyl)-4-chloro-5-iodo-pyrrolopyrimidine**: To a solution of 1 mMole of N7-((1'R,2'S,3'S,4'S)-2',3'-dihydroxy-4'-mercapto-cyclopentyl)-4-chloro-5-iodo-pyrrolopyrimidine in methanol is added 2 mMole of triethylamine and 1 mMole of 3-picolyl chloride hydrochloride. The mixture is slowly heated to reflux under nitrogen with stirring for one hour, then cooled and concentrated *in vacuo* . The residue is purified by flash chromatography to yield the title product.

EXAMPLE 53: Synthesis of **N7-((1'R,2'S,3'S,4'S)-2',3'-dihydroxy-4'-(pyridin-2''-yl)mercapto-cyclopentyl)-4-chloro-5-iodo-pyrrolo-pyrimidine**: To a solution of 1 mMole of N7-((1'R,2'S,3'S,4'S)-2',3'-dihydroxy-4'-mercapto-cyclopentyl)-4-chloro-5-iodo-pyrrolopyrimidine in ethanol is added 2 mMole of triethylamine and 1 mMole of 2-fluoropyridine. The mixture is slowly heated to reflux under nitrogen with stirring for 24 hours, then cooled and concentrated *in vacuo* . The residue is purified by flash chromatography to yield the title product.

EXAMPLE 54: Synthesis of **N7-((1'R,2'S,3'S,4'S)-2',3'-dihydroxy-4'-(methylmercapto)-cyclopentyl)-4-chloro-5-iodo-pyrrolopyrimidine**: To a solution of 1 mMole of N7-((1'R,2'S,3'S,4'S)-2',3'-dihydroxy-4'-mercapto-cyclopentyl)-4-chloro-5-iodo-pyrrolopyrimidine in methanol is added 2 mMole of triethylamine and 1 mMole of iodomethane. The mixture is slowly heated to reflux under nitrogen with stirring for 24 hours, then cooled and concentrated *in vacuo* . The residue is purified by flash chromatography to yield the title product.

EXAMPLE 55: Synthesis of **N7-((1'R,2'S,3'S,4'S)-2',3'-dihydroxy-4'-(pyridin-3'-yl)oxy-cyclopentyl)-4-chloro-5-iodo-pyrrolopyrimidine**: To a mixture of 135 mg of N7-((1'R,4'S)-cis-4'-(3'-pyridyl)oxy-2'-cyclopentenyl)-4-chloro-5-iodo-pyrrolopyrimidine, 108 mg of N-morpholine-N-oxide, and 0.5 mL of a 2.5% solution of osmium tetroxide in t-butanol at 0 °C is added tetrahydrofuran under nitrogen. The reaction was allowed to warm to 25 °C and stirred for two hours, then aqueous sodium sulfite was added and the reaction poured into dichloromethane and washed with a mixture of 10% sodium thiosulfate and sodium carbonate. The organic phase was dried (Na_2SO_4), concentrated

in vacuo, and purified by flash chromatography, eluting with methanol/ dichloromethane to give the title compound as a clear glass. $[a]_{25}^{D}$=-95.24 °(c = 0.4, methanol). Mass spectrum: $[M+H]^{+}$ m/z 473. IR (neat) 2850-3600 cm^{-1}.

EXAMPLE 56: Synthesis of **N7-((1'R,2'S,3'R,4'S)-2',3'-dihydroxy-4'-(t-butoxycarbonylamino)-cyclopentyl)-4-methoxy-5-iodo-pyrrolo-pyrimidine**: To a solution 1 mMole of N7-((1'R,2'S,3'R,4'S)-2',3'-dihydroxy-4'-(bis-t-butoxycarbonylamino)-cyclopentyl)-4-chloro-5-iodo-pyrrolopyrimidine in methanol is added 10 mMole of potassium methoxide. The solution is heated at 129 °C in a sealed vessel for 14 hours, then cooled. The methanol is removed by concentration *in vacuo* and the residue purified by flash chromatography to give the title product.

EXAMPLE 57: Synthesis of **N7-((1'R,2'S,3'R,4'S)-2',3'-dihydroxy-4'-(t-butoxycarbonylamino)-cyclopentyl)-4-methoxy-5-carbomethoxy-pyrrolopyrimidine**: A solution 1 mMole of N7-((1'R,2'S,3'R,4'S)-2',3'-dihydroxy-4'-(t-butoxycarbonylamino)-cyclopentyl)-4-methoxy-5-iodo-pyrrolo-pyrimidine, 0.05 mMole of palladium diacetate, and 0.2 mMole of tri-ortho-toluylphosphine in methanol is placed under 5 atmospheres of carbon monoxide. The solution is heated at 100 °C in a sealed vessel for 48 hours, then cooled. The methanol is removed by concentration *in vacuo* and the residue purified by flash chromatography to give the title compound

EXAMPLE 58: Synthesis of **N7-((1'R,2'S,3'R,4'S)-2',3'-dihydroxy-4'-(t-butoxycarbonylamino)-cyclopentyl)-4-methoxy-5-carboxy-pyrrolo-pyrimidine**: A solution 1 mMole of N7-((1'R,2'S,3'R,4'S)-2',3'-dihydroxy-4'-(t-butoxycarbonylamino)-cyclopentyl)-4-methoxy-5-carbomethoxy-pyrrolo-pyrimidine and 5 mMole of potassium hydroxide in aqueous tetrahydrofuran is heated at reflux until thin layer chromatography indicates complete ester hydrolysis, cooled, and the solvent removed *in vacuo*. The residue is suspended in aqueous methanol and carefully adjusted to pH 5 with aqueous hydrochloric acid. The mixture is diluted with saturated aqueous sodium chloride and extracted with dichloromethane. The organic phase is dried over Na_2SO_4, concentrated *in vacuo*, and the residue purified by flash chromatography to give the title compound.

EXAMPLE 59: Synthesis of **N7-((1'R,2'S,3'R,4'S)-2',3'-dihydroxy-4'-amino-cyclopentyl)-4-methoxy-5-(N-cyclobutyl-carboxamido)-pyrrolo-pyrimidine**: A solution of 1 mMole of N7-((1'R,2'S,3'R,4'S)-2',3'-dihydroxy-4'-(t-butoxycarbonylamino)-cyclopentyl)-4-methoxy-5-(N-cyclobutyl-carboxamido)-pyrrolo-pyrimidine was dissolved in trifluoroacetic acid at 10 °C and stirred for 10 minutes. The reaction was concentrated *in vacuo*, and purified by flash chromatography.

EXAMPLE 60: Synthesis of **N7-((1'R,2'S,3'R,4'S)-2',3'-dihydroxy-4'-amino-cyclopentyl)-4-amino-5-cyano-pyrrolopyrimidine**: x
A suspension of 1 mMole of N7-((1'R,2'S,3'R,4'S)-2',3'-dihydroxy-4'-amino-cyclopentyl)-4-amino-5-iodo-pyrrolopyrimidine and 20 mMole of copper(I) cyanide is heated in a sealed tube at 130 °C for six hours, then cooled, and the reaction concentrated *in vacuo*. The residue is purified by flash chromatography to give the title product.

EXAMPLE 61: Synthesis of **N7-((1'R,4'R)-trans-4'-hydroxy-2'-cyclopentenyl)-4-chloro-5-iodo-pyrrolopyrimidine**. To a suspension of 0.5 mmol of N7-((1'R,4'R)-trans-4'-hydroxy-2'-cyclopentenyl)-4-chloro-5-iodo-pyrrolopyrimidine in 2 mL of THF was added 0.6 mL of a 1.0 M solution of lithium hexamethyldisilazide in THF. After 5 minutes, 0.65 mmol of methanesulfonic anhydride was added as a solid. After 15 minutes, the solution of N7-((1'R,4'R)-trans-4'-(methanesulfonyl)oxy-2'-cyclopentenyl)-4-chloro-5-iodo-pyrrolopyrimidine was used immediately as a solution, or concentrated *in vacuo* for use.

EXAMPLE 62: Synthesis of **N7-((1'R,4'S)-cis-4'-(diphenylphosphinyl)-2'-cyclopentenyl)-4-chloro-5-iodo-pyrrolopyrimidine**: To a solution of 1 mMole of N7-((1'R,4'S)-trans-4'-(methanesulfonyl)oxy-2'-cyclopentenyl)-4-chloro-5-iodo-pyrrolo-pyrimidine in tetrahydrofuran at -78 °C is added 1 mMole of lithium diphenylphosphide. The mixture is allowed to warm to 25 °C over 2 hours, concentrated *in vacuo*, and treated with 2 mMole of 30% hydrogen peroxide. The mixture is heated at reflux for 30 minutes, cooled, concentrated *in vacuo*, and purified by flash chromatography to give the title compound.

EXAMPLE 63: Synthesis of **N7-((1'R,2'S,3'S,4'S)-2',3'-dihydroxy-4'-(diphenylphosphinyl)-cyclopentyl)-4-chloro-5-iodo-pyrrolo-pyrimidine**: To a

solution of 1 mMole of N7-((1'R,4'S)-cis-4'-(diphenyl-phosphinyl)-2'-cyclopentenyl)-4-chloro-5-iodo-pyrrolopyrimidine in t-butanol/ tetrahydrofuran at 10 °C is added 3 mMole of N-methylmorpholine-N-oxide and 0.2 mMole of solid osmium tetroxide. The mixture is allowed to warm to 25 °C, stirred for 12 hours, then poured into ethyl acetate and washed with a mixture of 10% sodium thiosulfate and sodium phosphate buffer (pH 7). The organic phase is dried (Na_2SO_4), concentrated *in vacuo*, and purified by flash chromatography to give the title compound.

EXAMPLE 64: Synthesis of **N7-((1'R,4'S)-cis-4'-(imidazol-1-yl)-2'-cyclopentenyl)-4-chloro-5-iodo-pyrrolopyrimidine**: To a solution of 1 mMole of N7-((1'R,4'S)-trans-4'-(methanesulfonyl)oxy-2'-cyclopentenyl)-4-chloro-5-iodo-pyrrolopyrimidine in dichloromethane at 0 °C is added 1 mMole of imidazole. The mixture is allowed to warm to 25 °C, stirred for 14 hours, concentrated *in vacuo*, and purified by flash chromatography.

EXAMPLE 65 Synthesis of **N7-((1'R,2'S,3'S,4'S)-2',3'-dihydroxy-4'-(imidazol-1-yl)-cyclopentyl)-4-chloro-5-iodo-pyrrolopyrimidine**: To a solution of 1 mMole of N7-((1'R,4'S)-cis-4'-N-imidazoyl-2'-cyclopentenyl)-4-chloro-5-iodo-pyrrolopyrimidine in t-butanol/tetrahydrofuran at 10 °C is added 3 mMole of N-methylmorpholine-N-oxide and 0.2 mMole of solid osmium tetroxide. The mixture is allowed to warm to 25 °C, stirred for 12 hours, concentrated *in vacuo*, and purified by flash chromatography, eluting with acetone/hexane to give the title compound.

EXAMPLE 66: Synthesis of **N7-((1'R,2'S,3'R,4'S)-2',3'-dihydroxy-4'-amino-cyclopentyl)-4-amino-5-methoxy-pyrrolopyrimidine**: A suspension of 1 mMole of N7-((1'R,2'S,3'R,4'S)-2',3'-dihydroxy-4'-amino-cyclopentyl)-4-amino-5-iodo-pyrrolopyrimidine, 10 mMole of sodium methoxide, and 0.1 mMole of copper(I) bromide in DMSO is heated in a sealed tube at 130 °C for six hours, cooled, and the reaction concentrated *in vacuo*. The residue is purified by flash chromatography to give the product.

EXAMPLE 67: Synthesis of **N7-((1'R,2'S,3'R,4'S)-2',3'-dihydroxy-4'-amino-cyclopentyl)-4,5-bis-phenylacetylenyl)-pyrrolopyrimidine**: A solution of 119 mg of N7-((1'R,2'S,3'R,4'S)-2',3'-dihydroxy-4'-(bis-t-butoxycarbonylamino)-

cyclopentyl)-4-chloro-5-iodo-pyrrolopyrimidine, 14 mg of bis(triphenylphosphine) palladium(II)dichloride, 7 mg of copper(I) iodide, 0.11 mL of phenylacetylene, and 4 mL of triethylamine in acetonitrile was heated at 70 °C for 17 hours. Concentration *in vacuo* gave a syrup which was purified by flash chromatography to give N7-((1'R,2'S,3'R,4'S)-2',3'-dihydroxy-4'-(bis-t-butoxycarbonylamino)-cyclopentyl)-4,5-bis-phenylacetylenyl)-pyrrolopyrimidine. This was dissolved in trifluoroacetic acid. After 20 minutes, the trifluoroaceti 8.11. Mass spectrum: $[M+H]^+$ m/z 435. IR (neat) 2800-3550, 2200, 1680, 1580 cm^{-1}.c acid was removed under vacuum, and resulting residue was co-evaporated from chloroform and ether, then suspended in water and lyophilized to give an orange solid, mp 82-86 °C. Analysis $(C_{27}H_{22}N_4O_2)$(2.0 trifluoroacetic acid)(2.6 H_2O) found: C 52.36, H 3.98, N 1

EXAMPLE 68: Synthesis of **N7-(((1'R,2'S,3'R,4'S)-2',3'-dihydroxy)-4'-amino-cyclopentyl)-4,5-bis-((2-phenyl)-ethyl))-pyrrolopyrimidine**: A suspension of 1 mMole of N7-(((1'R,2'S,3'R,4'S)-2',3'-dihydroxy)-4'-amino-cyclopentyl)-4,5-bis-phenylacetylenyl-pyrrolopyrimidine and 20 mg of 10% palladium on carbon in methanol is stirred under an atmosphere of hydrogen for two weeks. The mixture is filtered, concentrated *in vacuo,* and purified by flash chromatography to give the title product.

EXAMPLE 69: Synthesis of **N7-((1'R,2'S,3'R,4'S)-2',3'-dihydroxy-4'-amino-cyclopentyl)-4-phenylmercapto-5-iodo-pyrrolopyrimidine**: To a solution of 1 mMole of thiophenol and 1 mMole of potassium hydride in dimethylformamide is added 1 mMole of N7-((1'R,2'S,3'R,4'S)-2',3'-dihydroxy-4'-(bis-t-butoxycarbonylamino)-cyclopentyl)-4-chloro-5-iodo-pyrrolopyrimidine. The solution is heated at 100 °C in a sealed vessel for 14 hours, then cooled. The solvent is removed by concentration *in vacuo* and the residue purified by flash chromatography to give a single product. This is dissolved in trifluoroacetic acid and after stirring for 10 minutes at 25 °C, concentrated *in vacuo* and purified by flash chromatography to give the title compound.

EXAMPLE 70: Synthesis of **N7-((1'R,2'S,3'R,4'S)-2',3'-dihydroxy-4'-(4"-chlorobenzyl)amino-cyclopentyl)-4-phenylmercapto-5-iodo-pyrrolo-**

pyrimidine: To a solution of 1 mMole of N7-((1'R,2'S,3'R,4'S)-2',3'-dihydroxy-4'-amino-cyclopentyl)-4-phenylmercapto-5-iodo-pyrrolopyrimidine and 1 mMoles of 4-chlorobenzaldehyde in dimethylformamide/toluene is added 1 gram of 4Å molecular sieves. The mixture is heated at 50 °C with stirring for 12 hours, then cooled and concentrated *in vacuo*. This is treated with a 0.1 M solution of sodium borohydride in methanol for 1 hour, then concentrated *in vacuo* and purified by flash chromatography to give the title compound.

EXAMPLE 71: Synthesis of **N7-((1'R,2'S,3'S,4'S)-2',3'-O-(1-methylethylidene)-4'-(t-butyldimethylsilyloxy)-cyclopentyl)-4-chloro-pyrrolopyrimidine**: A mixture of 1 mMole of N7-((1'R,2'S,3'S,4'S)-2',3'-dihydroxy-4'-(t-butyldimethylsilyloxy)-cyclopentyl)-4-chloro-pyrrolopyrimidine, 3 mMole of 2,2-dimethoxypropane, and 0.02 mMole of 4-toluenesulfonic acid, in DMF is stirred at 25 °C for 24 hours. The reaction is then poured into ethyl acetate and washed with saturated sodium bicarbonate, dried over $MgSO_4$, and concentrated *in vacuo*. The residue is purified by flash chromatography.

EXAMPLE 72: Synthesis of **N7-((1'R,2'S,3'R,4'S)-2',3'-O-(1-methylethylidene)-4'-(t-butyldimethylsilyloxy)-cyclopentyl)-4-chloro-5-bromo-pyrrolopyrimidine**: A mixture of 1 mMole of N7-((1'R,2'S,3'S,4'S)-2',3'-O-(1-methylethylidene)-4'-(t-butyldimethylsilyloxy)-cyclopentyl)-4-chloro-pyrrolopyrimidine, and 1 mMole of N-bromosuccinimide in dichloromethane is stirred at 25 °C for 72 hours. The reaction is then poured into ethyl acetate and washed with a mixture of 10% sodium thiosulfate and saturated sodium bicarbonate, dried over $MgSO_4$, and concentrated *in vacuo*. The residue is purified by flash chromatography.

EXAMPLE 73: Synthesis of **N7-((1'R,2'S,3'S,4'S)-2',3'-O-(1-methylethylidene)-4'-hydroxy-cyclopentyl)-4-chloro-5-bromo-pyrrolo-pyrimidine**: A mixture of 1 mMole of N7-((1'R,2'S,3'S,4'S)-2',3'-O-(1-methylethylidene)-4'-(t-butyldimethylsilyloxy)-cyclopentyl)-4-chloro-5-bromo-pyrrolopyrimidine, and 2 mMole of tetra-(n-butyl)ammonium fluoride in tetrahydrofuran is stirred at 25 °C for 2 hours. The reaction is then concentrated *in vacuo* and the residue is purified by flash chromatography.

EXAMPLE 74: Synthesis of **N7-((1'R,2'S,3'S)-2',3'-O-(1-methylethylidene)-4'-oxo-cyclopentyl)-4-chloro-5-bromo-pyrrolo-pyrimidine**: To a mixture of 2 mMole of oxalyl chloride in dichloromethane at -60 °C is added 4 mMole of dimethylsulfoxide over 2 minutes. After 5 minutes, a solution of 1 mMole of N7-((1'R,2'S,3'R,4'S)-2',3'-O-(1-methylethylidene)-4'-hydroxy-cyclopentyl)-4-chloro-5-bromo-pyrrolopyrimidine in dichloromethane is added over 2 minutes, and after 15 minutes, 1 mMole of di-isopropyl-ethylamine is added over 2 minutes. The reaction is stirred at -60 °C for 20 minutes, then warmed to room temperature and poured into ethyl acetate/hexane and washed with saturated sodium bicarbonate solution, dried over $MgSO_4$, concentrated *in vacuo*, and purified by flash chromatography.

EXAMPLE 75: Synthesis of **N7-((1'R,2'S,3'R,4'S)-2',3'-O-(1-methylethylidene)-4'-(4"-dimethylaminobenzyl)amino-cyclopentyl)-4-chloro-5-bromo-pyrrolopyrimidine**: To a solution of 1 mMole of N7-((1'R,2'S,3'S)-2',3'-O-(1-methylethylidene)-4'-oxo-cyclopentyl)-4-chloro-5-bromo-pyrrolopyrimidine and 1 mMole of 4-(dimethylamino)benenzyl amine in dimethylformamide and toluene is added 4Å molecular sieves. The mixture is heated at 40 °C until imine formation is complete. The solution is cooled to 0 °C, and 5 mMole of a 0.25 M solution of sodium borohydride solution in ethanol is added with stirring. The reaction is maintained at 0 °C for one hour, quenched with water, then concentrated to a paste. This is diluted with dichloromethane, poured into dichloromethane and washed with sodium phosphate buffer (pH 7), dried over Na_2SO_4, and concentrated *in vacuo*. The residue is purified by flash chromatography to give the title product.

EXAMPLE 76: Synthesis of **N7-((1'R,2'S,3'R,4'S)-2',3'-dihydroxy-4'-(4"-dimethylaminobenzyl)amino-cyclopentyl)-4-chloro-5-bromo-pyrrolo-pyrimidine**: A solution of 1 mMole of N7-((1'R,2'S,3'R,4'S)-2',3'-O-(1-methylethylidene)-4'-(4"-dimethylaminophenyl)-cyclopentyl)-4-chloro-5-bromo-pyrrolo-pyrimidine in 1 N aqueous hydrochloric acid in tetrahydrofuran is stirred at 25 °C for two hours, then poured into dichloromethane and washed with sodium phosphate buffer (pH 7), dried over Na_2SO_4, and concentrated *in vacuo*. The residue is purified by flash chromatography to give the title product.

EXAMPLE 77: Synthesis of **N7-((1'R,2'S,3'S,4'S)-2',3'-O-(1-methyl-ethylidene)-4'-(t-butyldimethylsilyloxy)-cyclopentyl)-4-chloro-5-phenyl-pyrrolopyrimidine**: A mixture of 1 mMole of N7-((1'R,2'S,3'S,4'S)-2',3'-O-(1-methylethylidene)-4'-(t-butyldimethylsilyloxy)-cyclopentyl)-4-chloro-5-bromo-pyrrolo-pyrimidine, 1.2 mMole of phenyl-trimethylstannane, and 0.05 mMole of tetrakis-triphenylphosphine palladium (0) in DMF was heated at 70 °C for 12 hours, then cooled, and concentrated *in vacuo* to a dark syrup. The residue was purified by flash chromatography to give the title product.

EXAMPLE 78: Synthesis of **N7-((1'R,2'S,3'R,4'S)-2',3'-O-(1-methylethylidene)-4'-(t-butyldimethylsilyloxy)-cyclopentyl)-5-phenyl-pyrrolopyrimidine**: A mixture of 1 mMole of N7-((1'R,2'S,3'S,4'S)-2',3'-O-(1-methylethylidene)-4'-(t-butyldimethylsilyloxy)-cyclopentyl)-4-chloro-5-phenyl-pyrrolo-pyrimidine and 25 mg of 10% palladium on carbon in ethanol was hydrogenated under 3 atmospheres of hydrogen at 25 °C for one hour. The catalyst was removed by filtration, and the filtrate concentrated *in vacuo* . The residue was dissolved in tetrahydrofuran and treated with 1 mMole of tetra-(n-butyl)ammonium fluoride for 2 hours. The reaction was concentrated *in vacuo* and the residue was purified by flash chromatography to give the title product.

EXAMPLE 79: Synthesis of **N7-((1'R,2'S,3'S)-2',3'-O-(1-methylethylidene)-4'-oxo-cyclopentyl)-5-phenyl-pyrrolopyrimidine**: To a mixture of 2 mMole of oxalyl chloride in dichloromethane at -60 °C is added 4 mMole of dimethylsulfoxide over 2 minutes. After 5 minutes, a solution of 1 mMole of N7-((1'R,2'S,3'R,4'S)-2',3'-O-(1-methylethylidene)-4'-(t-butyldimethylsilyloxy)-cyclopentyl)-5-phenyl-pyrrolopyrimidine in dichloromethane is added over 2 minutes, and after 15 minutes, 1 mMole of di-isopropyl-ethylamine is added over 2 minutes. The reaction is stirred at -60 °C for 20 minutes, then warmed to room temperature and poured into ethyl acetate/hexane and washed with saturated sodium bicarbonate solution, dried over $MgSO_4$, concentrated *in vacuo*, and purified by flash chromatography.

EXAMPLE 80: Synthesis of **N7-((1'R,2'S,3'R,4'R)-2',3'-O-(1-methylethylidene)-4'-(4"-dimethylaminobenzyl)amino-cyclopentyl)-5-phenyl-pyrrolopyrimidine**: To a solution of 1 mMole of N7-((1'R,2'S,3'S)-

2',3'-O-(1-methylethylidene)-4'-oxo-cyclopentyl)-5-phenyl-pyrrolopyrimidine and 1 mMole of 4-(dimethylamino)benzyl amine in tetrahydrofuran and toluene is added 4Å molecular sieves. The mixture is heated at 40 °C until imine formation is complete. The solution is cooled to 0 °C, and 5 mMole of a 1 M solution of methyl magnesium bromide in ether is added with stirring. The reaction is maintained at 0 °C for two hours, then quenched with water and concentrated to a paste. This is diluted with dichloromethane, then poured into dichloromethane and washed with sodium phosphate buffer (pH 7), dried over Na_2SO_4, and concentrated *in vacuo*. The residue is purified by flash chromatography to give the title product.

EXAMPLE 81: Synthesis of **N7-((1'R,2'S,3'R,4'R)-2',3'-dihydroxy-4'-(4"-dimethylaminobenzyl)amino-cyclopentyl)-5-phenyl-pyrrolo-pyrimidine:** A solution of 1 mMole of N7-((1'R,2'S,3'R,4'R)-2',3'-O-(1-=methylethylidene)-4'-(4"-dimethylaminobenzyl)amino-cyclopentyl)-5-phenyl-pyrrolopyrimidine in 1 N aqueous hydrochloric acid in tetrahydrofuran is stirred at 25 °C for two hours, then poured into dichloromethane and washed with sodium phosphate buffer (pH 7), dried over Na_2SO_4, and concentrated *in vacuo*. The residue is purified by flash chromatography to give the title product.

EXAMPLE 82: Synthesis of **N7-((1'R,2'S,3'S)-2',3'-dihydroxy-4'-oxo-cyclopentyl)-5-phenyl-pyrrolopyrimidine:** A solution of 1 mMole of N7-((1'R,2'S,3'S)-2',3'-O-(1-methylethylidene)-4'-oxo-cyclopentyl)-5-phenyl-pyrrolo-pyrimidine in 1 N aqueous hydrochloric acid in tetrahydrofuran is stirred at 25 °C for two hours, then poured into dichloromethane and washed with sodium phosphate buffer (pH 7), dried over Na_2SO_4, and concentrated *in vacuo*. The residue is purified by flash chromatography to give the title product.

EXAMPLE 83: Synthesis of **N7-((1'R,2'S,3'S)-2',3'-dihydroxy-4'-oxo-cyclopentyl)-4-chloro-5-bromo-pyrrolopyrimidine:** A solution of 1 mMole of N7-((1'R,2'S,3'S)-2',3'-O-(1-methylethylidene)-4'-oxo-cyclopentyl)-4-chloro-5-bromo-pyrrolopyrimidine in 1 N aqueous hydrochloric acid in tetrahydrofuran is stirred at 25 °C for two hours, then poured into dichloromethane and washed with sodium phosphate buffer (pH 7), dried

over Na_2SO_4, and concentrated *in vacuo*. The residue is purified by flash chromatography to give the title product.

EXAMPLE 84: Synthesis of **N7-((1'R,4'S)-cis-4'-amino-2'-cyclo-pentenyl)-4-chloro-5-iodo-pyrrolopyrimidine**: A solution of 1 mMole of N7-((1'R,4'S)-cis-4'-(bis-t-butoxycarbonylamino)-2'-cyclopentenyl)-4-chloro-5-iodo-pyrrolopyrimidine in 5 mL of trifluoroacetic acid is stirred at 25 °C under nitrogen for 6 hours. The reaction is concentrated *in vacuo*, and the residue is then purified by flash chromatography, to give the title product.

EXAMPLE 85: Synthesis of **N7-((1'R,4'R)-cis-4'-amino-cyclopentyl)-4-chloro-5-iodo-pyrrolopyrimidine:** A solution of 200 mg of N7-((1'R,4'S)-cis-4'-(bis-t-butoxycarbonylamino)-2'-cyclopentenyl)-4-chloro-5-iodo-pyrrolopyrimidine, 35 mg of PtO_2, and 300 mg of $NaHCO_3$ in 20 mL of ethyl acetate was stirred under one atmosphere of hydrogen for 24 hours, after which time $MgSO_4$ was added, and solids removed by filtration. The filtrate was concentrated *in vacuo*, and the residue was purified by flash chromatography, eluting with methanol/dichloromethane. Fractions containing N7-((1'R,4'R)-cis-4'-(bis-t-butoxycarbonylamino)-2'-cyclopentyl)-4-chloro-5-iodo-pyrrolopyrimidine were combined and concentrated *in vacuo*, then dissolved in trifluoroacetic acid. After 20 minutes, the trifluoroacetic acid was removed *in vacuo*, and the residue partitioned between dichloromethane and 0.5 M potassium carbonate. The dichloromethane layer was dried over sodium sulfate, and concentrated *in vacuo*. The residue was purified by flash chromatography, eluting with 10% methanol/3% triethylamine/ dichloromethane, to give N7-((1'R,4'R)-cis-4'-amino-cyclopentyl)-4-chloro-5-iodo-pyrrolopyrimidine as a clear glass: Mass spectrum: $[M+H]^+$ m/z 362. IR (neat) 3250-3500, 1580 cm^{-1}. 1H NMR (300 MHz, DMSO/d_4-methanol) ∂ 8.61 (s, 1H), 8.02 (s, 1H), 3.77 (m, 1H), 2.86 (m, 1H), 2.05-2.17 (m, 5H).

EXAMPLE 86: Synthesis of **N7-((1'R,4'S)-4'-(imidazol-1-yl)-cyclopentyl)-4-chloro-pyrrolopyrimidine**: To a solution of 1 mMole of N7-((1'R,4'S)-cis-4'-N-imidazoyl-2'-cyclopentenyl)-4-chloro-5-iodo-pyrrolo-pyrimidine in methanol is added 50 mg of platinum oxide. The mixture is stirred at 25 °C under an atmosphere of hydrogen for 6 hours. The reaction is concentrated

in vacuo, and the residue is then purified by flash chromatography, to give the title product.

EXAMPLE 87: Synthesis of **N7-((1'R,4'S)-4'-(imidazol-1-yl)-cyclopentyl)-4-chloro-5-iodo-pyrrolopyrimidine**: To a solution of 1 mMole of N7-((1'R,4'S)-4'-(imidazol-1-yl)-cyclopentyl)-4-chloro-pyrrolo-pyrimidine and 2 mMole of anyhydrous sodium carbonate in dichloromethane is added 1 mMole of a 1-M solution of iodine monochloride in dichloromethane. The mixture is stirred at 25 °C under an atmosphere of nitrogen for 16 hours. The reaction is concentrated *in vacuo*, and the residue is then purified by flash chromatography, to give the title product.

EXAMPLE 88: Synthesis of **N7-((1'R,2'R,4'S)-4'-(t-butoxy-carbonylamino)-2'-hydroxy-cyclopentyl)-4-chloro-5-iodo-pyrrolo-pyrimidine and N7-((1'R,3'S,4'S)-4'-(t-butoxy-carbonylamino)-3'-hydroxy-cyclopentyl)-4-chloro-5-iodo-pyrrolopyrimidine**: To a solution of 1 mMole of N7-((1'R,4'S)-cis-4'-(bis-t-butoxycarbonylamino)-2'-cyclo-pentenyl)-4-chloro-5-iodo-pyrrolopyrimidine in tetrahydrofuran at 0 °C under nitrogen is added 3 mMoles of a 1-M solution of borane in tetrahydrofuran. The reaction is allowed to warm to 25 °C and stirred for 12 hours. The organoborane is oxidized by addition of 15 mMoles of N-methylmorpholine N-oxide. The reaction is monitored by thin layer chromatography until formation of the alcohol is complete. The reaction is concentrated *in vacuo*, and the residue is then purified by flash chromatography, to give the title products.

EXAMPLE 89: Synthesis of **N7-((1'R,2'R,4'S)-4'-amino-2'-hydroxy-cyclopentyl)-4-chloro-5-iodo-pyrrolopyrimidine**: A solution of 1 mMole of N7-((1'R,2'R,4'S)-4'-(t-butoxycarbonylamino)-2'-hydroxy-cyclopentyl)-4-chloro-5-iodo-pyrrolopyrimidine in 5 mL of trifluoroacetic acid is stirred at 25 °C under nitrogen for 6 hours. The reaction is concentrated *in vacuo*, and the residue is then purified by flash chromatography, to give the title product.

EXAMPLE 90: Synthesis of **N7-((1'R,3'S,4'S)-4'-amino-3'-hydroxy-cyclopentyl)-4-chloro-5-iodo-pyrrolopyrimidine**: A solution of 1 mMole of N7-((1'R,3'S,4'S)-4'-(t-butoxycarbonylamino)-3'-hydroxy-cyclopentyl)-4-chloro-5-iodo-pyrrolopyrimidine in 5 mL of trifluoroacetic acid is stirred at 25

°C under nitrogen for 6 hours. The reaction is concentrated *in vacuo*, and the residue is then purified by flash chromatography, to give the title product.

EXAMPLE 91: Synthesis of **N7-((1'R,2'R,4'S)-4'-(imidazol-1-yl)-2'-hydroxy-cyclopentyl)-4-chloro-5-iodo-pyrrolopyrimidine and N7-((1'R,3'S,4'S)-4'-(imidazol-1-yl)-3'-hydroxy-cyclopentyl)-4-chloro-5-iodo-pyrrolo-pyrimidine**: To a solution of 1 mMole of N7-((1'R,4'S)-cis-4'-(imidazol-1-yl)-2'-cyclopentenyl)-4-chloro-5-iodo-pyrrolo-pyrimidine in tetra-hydrofuran at 0 °C under nitrogen is added 3 mMoles of a 1-M solution of borane in tetrahydrofuran. The reaction is allowed to warm to 25 °C and stirred for 12 hours. The organoborane is oxidized by addition of 15 mMoles of N-methylmorpholine N-oxide. The reaction is monitored by thin layer chromatography until formation of the alcohol is complete. The reaction is concentrated *in vacuo*, and the residue is then purified by flash chromatography, to give the title products.

EXAMPLE 92: **N7-((1'R,2'S,3'R,4'S)-2',3'-dihydroxy-4'-(2''-pyrimidinyl)-amino-cyclopentyl)-4-amino-5-iodo-pyrrolopyrimidine**: In accordance with the method for Example 42, a suspension of 94 mg of N7-((1'R,2'S,3'R,4'S)-2',3'-dihydroxy-4'-amino-cyclopentyl)-4-amino-5-iodo-pyrrolopyrimidine, 172 mg of 2-chloropyrimidine, and 96 mg of diisopropylethylamine in 3 mL of N-methylpyrrolidinone was heated at 80 °C for 20 hours, then cooled. The precipitate formed by pouring the reaction into ethyl acetate was filtered and washed with methanol, followed by ethyl acetate. The organic layer was concentrated *in vacuo*, and the residue was purified by flash chromatography, eluting with methanol/dichloromethane to give the product as a white powder, mp 202-210 °C. Mass spectrum $[M+H]^+$ m/z 454. IR (neat) 3550,3430, 3250, 3180, 1650, 1580 cm^{-1}.

EXAMPLE 93: Synthesis of **N7-((1'R,2'S,3'R,4'S)-2',3'-dihydroxy-4'-(2''-pyridinylacetyl)amino-cyclopentyl)-4-chloro-5-iodo-pyrrolopyrimidine**: A solution of 38 mg of 2-pyridinyl acetic acid and 35 mg of carbonyl diimidazole was stirred in 2 mL of DMF for 40 minutes to prepare a solution of N-(2-pyridinylacetyl) imidazole.

A solution of 165 mg of N7-((1'R, 2'S, 3'R, 4'S)-2',3'-bis-(t-butyldimethylsilyloxy)-4'-(bis-t-butoxycarbonylamino)cyclopentyl)-4-chloro-5-iodo-pyrrolopyrimidine was dis- solved in 2 mL of trifluoroacetic acid. After 5 minutes, the solvent was removed under vacuum to give a glassy residue. To this residue was added the DMF solution of N-(2-pyridinyl-acetyl) imidazole prepared above. After stirring for one hour, the reaction was poured into saturated sodium bicarbonate and extracted with ethyl acetate. The organic phase was dried over sodium sulfate and purified by flash chromatography, eluting with ethyl acetate/hexane to give N7-((1'R, 2'S, 3'R, 4'S)-2',3'-bis-(t-butyldimethylsilyloxy)-4'-(2-pyridinylacetyl)cyclopentyl)-4-chloro-5-iodo-pyrrolopyrimidine as a yellow powder. This was dissolved in THF and 0.12 mL of tetrabutylammonium fluoride (1 M in THF) was added. After six hours, the reaction mixture was poured into wate and extracted with ethyl acetate. After drying over sodium sulfate, the organic phase was concentrated *in vacuo* and purified by flash chromatography, eluting with 10% methanol/dichloromethane to give the product as a white powder, mp 95-107°C. Mass spectrum $[M+H]^+$ m/z 514. IR (neat) 3000-3600, 1650, 1580, 1530 cm^{-1}.

EXAMPLE 94: Synthesis of **N7-((1'R,2'S,3'R,4'S)-2',3'-dihydroxy-4'-(dimethylaminoacetyl)amino-cyclopentyl)-4-chloro-5-iodo-pyrrolo-pyrimidine:** A solution of 90 mg of N7-((1'R,2'S,3'R,4'S)-2',3'-dihydroxy-4'-(aminoacetyl)amino-cyclopentyl)-4-chloro-5-iodo-pyrrolopyrimidine, 0.045 mL of 37% formaldehyde, and 28 mg of sodium cyanoborohydride in 1.5 mL of 0.1 M aqueous sodium dihydrogen phosphate and methanol was stirred for 24 hours, then poured into water and extracted with ethyl acetate. The organic phase was dried over sodium sulfate, concentrated *in vacuo*, and purified by chromatography on silica gel, eluting with acetonitrile/dichloromethane, to give a white powder, mp 152-156 °C. Analysis ($C_{15}H_{19}N_5O_3ICl$) found: C 37.40, H 4.04, N 14.34. Mass spectrum (FAB) $[M+H]^+$ m/z 480. IR (neat) 3150-3600, 1660, 1650, 1580, 1530 cm^{-1}.

EXAMPLE 95: Synthesis of **N7-((1'R,2'S,3'R,4'S)-2',3'-dihydroxy-4'-(3"-pyridinylacetyl)amino-cyclopentyl)-4-chloro-5-iodo-pyrrolopyrimidine:** By the method used to prepare N7-((1'R,2'S,3'R,4'S)-2',3'-dihydroxy-4'-(2"-pyridinylacetyl)amino-cyclopentyl)-4-chloro-5-iodo-pyrrolopyrimidine, the

title product was prepared as a white powder, mp 190-210 °C. Mass spectrum $[M+H]^+$ m/z 514. IR (neat) 3000-3600, 1640, 1580, 1530 cm^{-1}.

EXAMPLE 96: Synthesis of **N7-((1'R,2'S,3'R,4'S)-2',3'-dihydroxy-4'-(N-t-butoxycarbonylaminoacetyl)amino-cyclopentyl)-4-chloro-5-iodo-pyrrolo-pyrimidine:** A solution of 165 mg of N7-((1'R, 2'S, 3'R, 4'S)-2',3'-bis-(t-butyl-dimethylsilyloxy)-4'-(bis-t-butoxycarbonylamino)cyclopentyl)-4-chloro-5-iodo-pyrrolopyrimidine was dissolved in 2 mL of trifluoroacetic acid. After 5 minutes, the solvent was removed under vacuum to give a glassy residue. To this residue was added 60 mg of N-t-butoxycarbonylamino-glycine hydroxysuccinimide ester, 0.14 mL of triethylamine, and 1 mL of pyridine. After stirring for six hours, the reaction was poured into saturated sodium bicarbonate and extracted with ethyl acetate. The organic phase was dried over sodium sulfate and purified by flash chromatography, eluting with ethyl acetate/hexane to give N7-((1'R, 2'S, 3'R, 4'S)-2',3'-bis-(t-butyldi-methylsilyloxy)4'-(N-t-butoxycarbonylaminoacetyl)cyclopentyl)-4-chloro-5-iodo-pyrrolopyrimidine as a glass. This was dissolved in THF and 0.12 mL of tetrabutylammonium fluoride (1 M in THF) was added. After three days, the reaction was poured into water and extracted with ethyl acetate. After drying over sodium sulfate, the organic phase was concentrated *in vacuo* and purified by flash chromatography, eluting with 10% methanol/dichloromethane to give the product as a white powder, mp 195 °C. Mass spectrum (FAB) $[M+H]^+$ m/z 552.

EXAMPLE 97: Synthesis of **N7-((1'R,2'S,3'R,4'S)-2',3'-dihydroxy-4'-(amino-acetyl)amino-cyclopentyl)-4-chloro-5-iodo-pyrrolopyrimidine:** A solution of 210 mg of N7-((1'R,2'S,3'R,4'S)-2',3'-dihydroxy-4'-(N-t-butoxycarbonyl-aminoacetyl)amino-cyclopentyl)-4-chloro-5-iodo-pyrrolopyrimidine in tri-fluoroacetic acid was stirred for 20 minutes, the solvent was removed *in vacuo*, and excess trifluoroacetic acid was removed by co-evaporation with chloroform, to give the product as a white powder, mp 147-157 °C. Analysis $(C_{13}H_{15}N_5O_3ICl)(CF_3CO_2H\cdot)(0.5H_2O)$ found: C 30.67, H 2.88, N 11.18. Mass spectrum (FAB) $[M+H]^+$ m/z 452.

EXAMPLE 98: Synthesis of **N7-((1'R,2'S,3'R,4'S)-2',3'-dihydroxy-4'-(4"-bromo phenyl)amino-cyclopentyl)-4-chloro-5-iodo-pyrrolopyrimidine:** A solution of

0.69 g of 4-bromoaniline and 0.88 g of di-t-butyl dicarbonate in dichloromethane was stirred for two days, then purified by flash chromatography to give 4-bromo-N-butoxycarbonylaniline.

A solution of 204 mg of 4-bromo-N-butoxycarbonylaniline in THF was deprotonated by adding 0.75 mL of a solution of lithium hexamethyldisilazide (1 M in toluene). This solution was added to a solution of 220 mg of N7-((1'R,4'R)-trans-4'-(methanesulfonyl)oxy-2'-cyclopentenyl)-4-chloro-5-iodo-pyrrolopyrimidine in dichloromethane in THF. After two days, the reaction was concentrated *in vacuo* and purified by flash chromatography, eluting with ethyl/dichloromethane, to give N7-((1'R,4'S)-cis-4'-(4"-bromo phenyl)amino-2'-cyclopentenyl)-4-chloro-5-iodo-pyrrolopyrimidine.

A solution of 185 mg of N7-((1'R,4'S)-cis-4'-(N-4"-bromo phenyl-N-(t-butoxycarbonyl))amino-2'-cyclopentenyl)-4-chloro-5-iodo-pyrrolopyrimidine, 105 mg of N-methylmorpholine-N-oxide, and 0.15 mmol of osmium tetroxide in t-butanol/THF/isopropanol was stirred for two days, then treated with sodium sulfite solution, poured into water, and extracted with ethyl acetate. The organic phase was dried over sodium sulfate, concentrated *in vacuo*, and purified by flash chromatography, eluting with ethyl acetate/hexane to give N7-((1'R,2'S,3'R,4'S)-2',3'-dihydroxy-4'-(N-4"-bromo phenyl-N-(t-butoxycarbonyl))amino-cyclopentyl)-4-chloro-5-iodo-pyrrolopyrimidine as a white solid.

A solution of 71 mg of N7-((1'R,2'S,3'R,4'S)-2',3'-dihydroxy-4'-(N-4"-bromo phenyl-N-(t-butoxycarbonyl))amino-cyclopentyl)-4-chloro-5-iodo-pyrrolopyrimidine in trifluoroacetic acid was stirred for 20 minutes, then concentrated *in vacuo*. Excess trifluoroacetic acid was removed by coevaporation with toluene to give a white solid, mp 112-125 °C. Analysis ($C_{17}H_{15}N_4O_2IBrCl$)(0.5 trifluoroacetic acid)(1.5 SiO_2) found: C 31.03, H 2.24, N 8.04. $[a]_D^{25}$=-29.03 °(c=0.3, ethyl acetate). Mass spectrum: $[M+H]^+$ m/z 549. IR (neat) 2300-3600, 1590, 1580 cm^{-1}.

EXAMPLE 99: Synthesis of **N7-((1'R,4'R)-cis-4'-amino-cyclopentyl)-4-chloro-5-iodo-pyrrolopyrimidine:** A solution of 200 mg of N7-((1'R,4'S)-cis-4'-(bis-t-butoxycarbonylamino)-2'-cyclopentenyl)-4-chloro-5-iodo-pyrrolopyrimidine,

35 mg of PtO_2, and 300 mg of $NaHCO_3$ in 20 mL of ethyl acetate was stirred under one atmosphere of hydrogen for 24 hours, after which time $MgSO_4$ was added, and solids removed by filtration. The filtrate was concentrated *in vacuo*, and the residue was purified by flash chromatography, eluting with methanol/dichloromethane. Fractions containing N7-((1'R,4'R)-cis-4'-(bis-t-butoxycarbonylamino)-2'-cyclopentyl)-4-chloro-5-iodo-pyrrolopyrimidine were combined and concentrated *in vacuo*, then dissolved in trifluoroacetic acid. After 20 minutes, the trifluoroacetic acid was removed *in vacuo*, and the residue partitioned between dichloromethane and 0.5 M potassium carbonate. The dichloromethane layer was dried over sodium sulfate, and concentrated *in vacuo*. The residue was purified by flash chromatography, eluting with 10% methanol/3% triethylamine/ dichloromethane, to give N7-((1'R,4'R)-cis-4'-amino-cyclopentyl)-4-chloro-5-iodo-pyrrolopyrimidine as a clear glass: Mass spectrum: $[M+H]^+$ m/z 362. IR (neat) 3250-3500, 1580 cm^{-1}. 1H NMR (300 MHz, DMSO/d_4-methanol) ∂ 8.61 (s, 1H), 8.02 (s, 1H), 3.77 (m, 1H), 2.86 (m, 1H), 2.05-2.17 (m, 5H).

EXAMPLE 100: Synthesis of **N7-((1'R,2'S,3'R,4'S)-2',3'-dihydroxy-4'-(bis-t-butoxycarbonylamino)-cyclopentyl)-4-chloro-5-phenyl-pyrrolopyrimidine**: A mixture of 250 mg of N7-((1'R,2'S,3'R,4'S)-2',3'-dihydroxy-4'-(bis-t-butoxy-carbonylamino)-cyclopentyl)-4-chloro-5-iodo-pyrrolopyrimidine, 132 mg of phenyltrimethylstannane, and 20 mg of dibenzylidineacetone palladium (0), and 26 mg of triphenylarsine in DMF was heated at 70 °C for 16 hours, then cooled, poured into water and extracted with dichloromethane. The organic phase was dried over sodium sulfate, and concentrated *in vacuo* to a dark syrup. The residue was purified by flash chromatography, eluting with ethyl acetate/dichloromethane to give the title product. $[a]_{25}^{D}$=+4.17°(c = 0.7, dichloromethane). Mass spectrum: $[M+H]^+$ m/z 545. IR (neat) 1740, 1700 cm^{-1}.

EXAMPLE 101: Synthesis of **N7-((1'R,2'S,3'R,4'S)-2',3'-dihydroxy-4'-amino-cyclopentyl)-4-chloro-5-phenyl-pyrrolopyrimidine**: A mixture of 165 mg of N7-((1'R,2'S,3'R,4'S)-2',3'-dihydroxy-4'-(bis-t-butoxycarbonylamino)-cyclopentyl)-4-chloro-5-phenyl-pyrrolopyrimidine, 0.75 mL of aniline, and dioxane was heated in a sealed tube at 135 °C for 24 hours, then cooled and poured into ethyl acetate/dichloromethane, then washed with aqueous potassium

carbonate. The organic phase was dried over sodium sulfate, concentrated *in vacuo*, and purified by chromatography, eluting with ethyl acetate/dichloromethane to give a clear glass. This was dissolved in trifluoroacetic acid and after ten minutes, concentrated *in vacuo*, then purified by flash chromatography, eluting with acetonitrile/acetic acid/water to give a brown glass. This was dissolved in 4 M HCl, then lyophilized to remove water and give a brown powder.$[a]_{25}^{D}$=-14.38 °(c = 0.7, methanol). Mass spectrum: $[M+H]^+$ m/z 402. IR (neat) 2800-3650 cm^{-1}.

EXAMPLE 102: Synthesis of **N7-((1'R,2'S,3'R,4'S)-2',3'-dihydroxy-4'-(t-butoxycarbonyl-methylene)amino-cyclopentyl)-4-chloro-5-iodo-pyrrolo-pyrimidine:** A solution of 550 mg of N7-((1'R, 2'S, 3'R, 4'S)-2',3'-bis-(t-butyldimethylsilyloxy)-4'-(bis-t-butoxycarbonylamino)cyclopentyl)-4-chloro-5-iodo-pyrrolopyrimidine was dissolved in 4 mL of trifluoroacetic acid. After 20 minutes, the solvent was removed under vacuum to give a glassy residue. To this residue was dichloromethane, triethylamine, and 0.5 mL of ethyl bromoacetate. After 14 hours, the reaction was concentrated *in vacuo*, and purified by flash chromatography, eluting with ethyl acetate/ dichloromethane to give a white foam, N7-((1'R, 2'S, 3'R, 4'S)-2',3'-bis-(t-butyldimethylsilyloxy)-4'-(t-butoxycarbonyl-methylene)cyclopentyl)-4-chloro-5-iodo-pyrrolopyrimidine. This was dissolved in THF and treated with tetrabutylammonium fluoride. After one hour, the reaction was concentrated *in vacuo* and purified by flash chromatography, eluting with ethanol/dichloromethane to give a white powder, mp 170-175. Analysis: $(C_{17}H_{22}N_4O_4ICl)(0.4\ H_2O)$ found: C 39.89, H 4.38, N 10.66. Mass spectrum: $[M+H]^+$ m/z 511. IR (neat) 3000-3580, 1725 cm^{-1}.

EXAMPLE 103: Synthesis of **N7-((1'R,2'S,3'R,4'S)-2',3'-dihydroxy-4'-(carboxy-methylene)amino-cyclopentyl)-4-chloro-5-iodo-pyrrolopyrimidine:** A solution of 164 mg of N7-((1'R,2'S,3'R,4'S)-2',3'-dihydroxy-4'-(t-butoxycarbonyl-methylene)amino-cyclopentyl)-4-chloro-5-iodo-pyrrolo-pyrimidine was dissolved in 5 mL of trifluoroacetic acid. After 150 minutes, the solvent was removed under vacuum to give a glassy residue. This was coevaporated with methanol/chloroform to give a brittle glass, mp 155 °C (decomposition). $[a]_{25}^{D}$=-15.99 ° (c = 0.9, methanol). Analysis:

($C_{13}H_{14}N_4O_4ICl$)(1.7 trifluoroacetic acid) found: C 30.68, H 2.84, N 8.41. Mass spectrum: $[M+H]^+$ m/z 453. IR (neat) 2800-3600, 1790, 1735, 1675 cm^{-1}.

EXAMPLE 104: Synthesis of **N7-((1'R,4'S)-4'-((N-(2",4"-dinitrophenyl-sulfonyl)-(O-t-butyl)-L-asparaginyl)cyclopentenyl)-4-chloro-5-iodo-pyrrolo-pyrimidine**: A mixture of 0.95 g of t-butyl-L-asparagine hydrochloride, 1.26 g of 2,4-dinitrophenylsulfonyl chloride, and 0.9 g of 2,6-lutidine in dichloromethane was stirred for eight hours, then purified by chromatography, eluting with ethyl acetate to give N^1-2',4'-dinitrophenylsulfonyl-L-asparagine t-butyl ester. A mixture of 0.65 g of N^1-2',4'-dinitrophenylsulfonyl-L-asparagine t-butyl ester, 0.37 g of N7-((1'R,4'R)-trans-4'-hydroxy-2'-cyclopentenyl)-4-chloro-5-iodo-pyrrolopyrimidine, 0.41 g of triphenylphosphine, and 0.36 g of di-t-butyl azodicarboxylate in toluene was stirred for two days, then purified by flash chromatography, eluting with methanol/dichloromethane, then ethyl acetate/hexane to give the product $[a]25^D$=+32.10° (c = 1.0, chloroform). Analysis: ($C_{25}H_{25}N_7O_9ICl$)(0.6 chloroform) found: C 36.89, H 3.12, N 11.44. Mass spectrum: $[M+H]^+$ m/z 762. IR (neat) 3480, 3400, 1735, 1685 cm^{-1}.

EXAMPLE 105: Synthesis of **N7-((1'R,2'S,3'R,4'S)-2',3'-dihydroxy-4'-(N-(2",4"-dinitrophenylsulfonyl)-O-t-butyl-L-asparaginyl)cyclopentyl)-4-chloro-5-iodo-pyrrolopyrimidine**: A mixture of 439 mg of N7-((1'R,4'S)-4'-((N-(2",4"-dinitrophenylsulfonyl)-(O-t-butyl)-L-asparaginyl)cyclopentenyl)-4-chloro-5-iodo-pyrrolopyrimidine, 270 mg N-methyl-morpholine-N-oxide, and 1 mL of 2.5% of osmium tetroxide in t-butanol in THF was stirred for two days, then treated with 10% sodium sulfite, poured into water and extracted with dichloromethane/ethyl acetate. The organic phase was dried over sodium sulfate, and purified by chromatography, eluting with ethanol/dichloromethane then coevaporation with toluene to give the product as a white solid, mp 175 °C (decomposition). $[a]25^D$=+26.32 ° (c = 0.5, dichloromethane). Analysis: ($C_{25}H_{27}N_7O_{11}SICl$)(0.2 toluene) found: C 38.74, H 3.56, N 11.87. Mass spectrum (FAB): $[M+H]^+$ m/z 834. IR (neat) 3390, 3480, 1730, 1670 cm^{-1}.

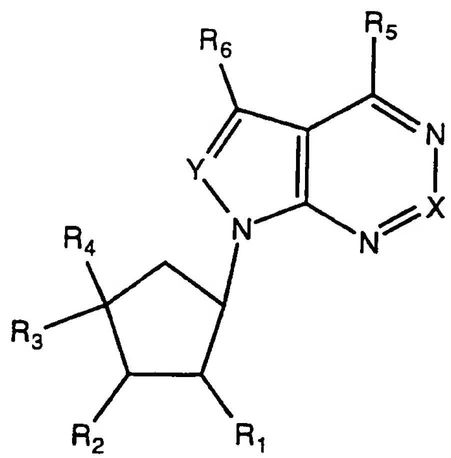
EXAMPLE 106: Synthesis of **N7-((1'R,2'S,3'R,4'S)-2',3'-dihydroxy-4'-(N-(O-t-butyl)-L-asparaginyl)cyclopentyl)-4-chloro-5-iodo-pyrrolopyrimidine**: A

mixture of 230 mg of N7-((1'R,2'S,3'R,4'S)-2',3'-dihydroxy-4'-(N-(2",4"-dinitrophenylsulfonyl)-(O-t-butyl)-L-asparaginyl)cyclopentyl)-4-chloro-5-iodo-pyrrolopyrimidine and 0.5 mL of propylamine in acetonitrile was stirred for 90 minutes, then concentrated *in vacuo,* and purified by chromatography, eluting with ethanol/dichloromethane to give the product as a clear glass. $[a]25^{D}$=-34.10 ° (c = 0.7, methanol). Analysis: ($C_{19}H_{25}N_5O_5ICl$)(0.3 ethanol)(0.7 H_2O) found: C 39.75, H 4.58, N 11.59. Mass spectrum: $[M+H]^+$ m/z 566. IR (neat) 3150-3600, 1720, 1660 cm^{-1}.

EXAMPLE 107: Synthesis of **N7-((1'R,2'S,3'R,4'S)-2',3'-dihydroxy-4'-(N-asparaginyl)cyclopentyl)-4-chloro-5-iodo-pyrrolopyrimidine**: A mixture of 53 mg of N7-((1'R,2'S,3'R,4'S)-2',3'-dihydroxy-4'-(N-(O-t-butyl)-L-asparaginyl)-cyclopentyl)-4-chloro-5-iodo-pyrrolopyrimidine in 8 mL of trifluoroacetic acid was stirred for two hours, concentrated *in vacuo,* coevaporated with acetonitrile/acetic acid/water, then lyophilized from water to give a white foam. $[a]25^{D}$=-39.73 ° (c = 0.06, methanol). Analysis: ($C_{15}H_{17}N_4O_5ICl$)(3 trifluoroacetic acid)(4.4 H_2O)(5 acetonitrile) found: C 32.71, H 3.40, N 11.64. Mass spectrum: $[M+H]^+$ m/z 510. IR (neat) 2800-3600, 1675, 1630, 1575 cm^{-1}.

WHAT IS CLAIMED IS:

1. A compound of the Formula I



Formula I

wherein

X is -N or -CR_7 where R_7 is hydrogen, halogen, loweralkyl, loweralkoxy or -S-loweralkyl;

Y is -N or -CH;

R_1 and R_2 are each independently hydrogen, hydroxy, alkoxy, or acyloxy or R_1 and R_2 are both hydroxy protected with an individual hydroxy protecting group or with a single dihydroxy-protecting group or R_1 and R_2 are absent and there is a double bond between the carbon atoms to which R_1 and R_2 are attached;

R_3 is hydrogen, hydroxy, loweralkyl or alkoxy;

R_4 is a) hydrogen, b) amino, c) halogen, d) hydroxy, e) sufonamido, f) -P(O)$(OH)_2$, g) -P(O)-R_8R_9 wherein R_8 and R_9 are each independently hydrogen, hydroxy, loweralkyl, aryl, or arylalkyl, h) -NHR_{10} wherein R_{10} is hydrogen or an amino protecting group, i) -NHC(O)NHR_{11} where R_{11} is hydrogen or loweralkyl, or j) -A-R_{12} wherein A is O, $S(O)_n$ or -$N(R_{13})$- wherein R_{13} is hydrogen or loweralkyl, n is zero, one or two, and R_{12} is hydrogen, loweralkyl, alkylsulfonyl, acyl, alkoxycarbonyl, aryl, heteroaryl, arylalkyl, arylsulfonyl, haloalkyl, heteroarylalkyl, heteroarylsulfonyl, aminoalkyl or heterocyclic or k) R4 is a ring N-member of a heteroaryl or heterocycle; or

R_3 and R_4 taken together are =O, or taken together with the carbon atom to which they are attached, form a spirocyclic ring;

R_5 is hydrogen, loweralkyl, aryl, arylalkyl, heteroaryl, amino, alkylamino, alkoxy, acylamino, arylalkynyl, arylamino, arylmercapto, alkylmercapto, halogen, heterocyclic, hydrazino, -NHC(O)NH_2, or -$NR_{14}R_{15}$ wherein R_{14} and R_{15} are each independently hydrogen or an amino protecting group or -$NR_{14}R_{15}$ is a nitrogen containing heterocycle of 5 to 7 members; and

R_6 is loweralkyl, cycloalkyl, alkenyl, alkynyl, alkoxy, alkoxycarbonyl, carboxy, aryl, heteroaryl, heteroarylalkyl, arylalkyl, arylalkenyl, arylalkynyl, cyano, halogen, heteroarylalkynyl, or -C(O)NHR_{16} wherein R_{16} is alkyl, aryl, or heterocyclic.

2. A compound according to Claim 1 wherein X is -CH.

3. A compound according to Claim 1 or 2 wherein R_1 and R_2 are -OH.

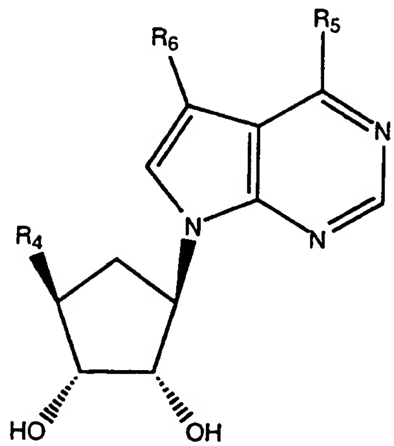
4. A compound according to any of Claims 1 to 3 wherein R_4 is amino, hydroxyl, -NHR_{10} or -$NR_{12}R_{13}$ where R_{10}, R_{12} and R_{13} are as defined in claim 1.

5. A compound according to any of Claims 1 to 4 wherein R_6 is aryl, arylalkyl, arylalkenyl, arylalkynyl, or halogen.

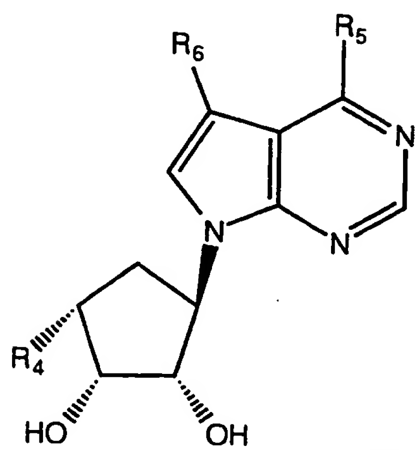
6. A compound according to Claim 1 wherein X is -CH; R_1 and R_2 are -OH; R_4 is amino, hydroxyl, -NHR_{10} or -$NR_{12}R_{13}$ where R_{10}, R_{12} and R_{13} are as defined in claim 1, R_5 is amino, arylalkyl, arylalkynyl, arylamino or halogen and R_6 is aryl, arylalkyl, arylalkenyl, arylalkynyl, or halogen.

7. A compound according to Claim 1 wherein R_3 is hydrogen and R_4 is hydroxy, or -NHR_{10} wherein R_{10} is hydrogen or an amino protecting group.

8. A compound according to claim 1 having the Formula III or IV, below



Formula III



Formula V

wherein R_4, R_5, and R_6 are as defined in claim 1.

9. A compound according to Claim 8 wherein R_4 is amino, hydroxyl, $-NHR_{10}$ or $-NR_{12}R_{13}$ where R_{10}, R_{12} and R_{13} are as defined in claim 1, R_5 is amino, arylalkyl, arylalkynyl, arylamino or halogen and R_6 is aryl, arylalkyl, arylalkenyl, arylalkynyl, or halogen.

10. A compound according to Claim 8 or 9 wherein R_4 is amino, methylamino, dimethylamino, carbamate, acylamino or heteroarylacylamino.

11. A compound according to any of Claims 8 to 10 wherein R_6 is chloro, iodo, phenyl, 2-phenylethyl or 2-phenylethynyl.

12. A compound according to Claim 8 wherein R_4 is amino, methylamino, dimethylamino, carbamate, acylamino or heteroarylacylamino; R_5 is chloro, amino, phenylamino or 2-phenylethynyl; and R_6 is chloro, iodo, phenyl, 2-phenylethyl or 2-phenylethynyl.

13. A compound according to claim 12 wherein R_4 is hydroxyl and the values of R_5 and R_6 are:

a) R_5 is Cl and R_6 is Cl, I, phenyl, or 2-phenylethynyl;

b) R_5 is NH2 and R_6 is I, phenyl, 2-phenylethyl or 2-phenylethynyl;

c) R_5 is phenylamino and R_6 is I or phenyl;

d) R_5 is 2-phenylethynyl and R_6 is 2-phenylethynyl.

14. A compound according to claim 12 wherein:

a) R_4 is NH_2, R_5 is Cl or NH_2 and R_6 is I;

b) R_4 is Boc_2N, R_5 is Cl and R_6 is I;

c) R_4 is NHBoc, R_5 is NH_2 and R_6 is I;

d) R_4 is CH_3NH, R_5 is Cl and R_6 is CH_3;

e) R_4 is $(CH_3)_2N$, R_5 is Cl and R_6 is I;

f) R_4 is nicotinamide, R_5 is Cl and R_6 is I;

g R_4 is (3''-chloro-pyridazin-6''-yl)amino, R_5 is NH2, and R_6 is I;

h) R_4 is (2''-pyrimidinyl)amino, R_5 is NH2, and R_6 is I;

i) R_4 is (3''-pyridinylacetyl)amino, R_5 is Cl and R_6 is I;

j) R_4 is (N-t-butoxycarbonylaminoacetyl) amino, R_5 is Cl, and R_6 is I;

k) R_4 is (aminoacetyl)amino, R_5 is Cl, and R_6 is I;

l) R_4 is (dimethylaminoacetyl)amino, R_5 is Cl and R_6 is I;

m) R_4 is (4''-bromophenyl)amino, R_5 is Cl and R_6 is I;

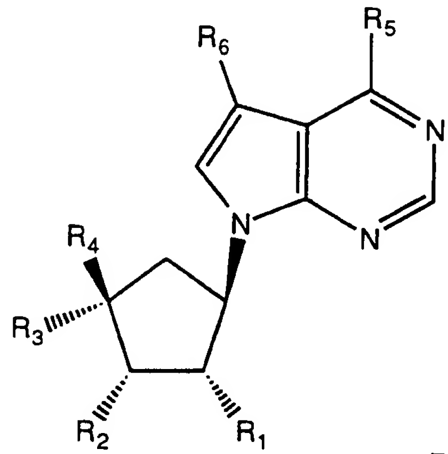
n) R_4 is (pyridine-3''-yl)oxy, R_5 is Cl, and R_6 is I;

o) R_4 is bis-(t-butoxycarbonyl-methylene)amino, R_5 is Cl and R_6 is I;

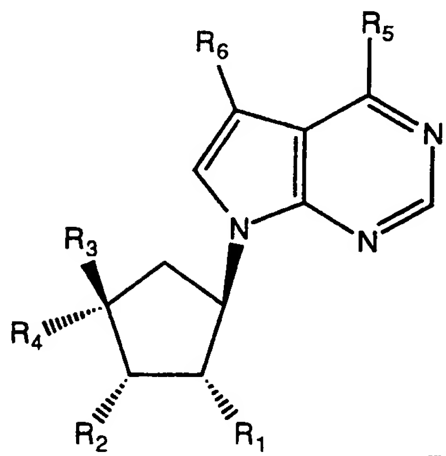
p) R_4 is (carboxy-methylene)amino, R_5 is Cl, and R_6 is I; and

q) R_4 is N-(2'',4''-dinitrophenylsulfonyl)-(O-t-butyl)-L-asparaginyl, R_5 is Cl and R_6 is I.

15. A compound according to claim 1 having the Formula II or IV



Formula II



Formula IV

wherein R_1, R_2, R_3, R_4, R_5 and R_6 are as defined in claim 1.

16. A compound according to Claim 15 wherein R_4 is amino, hydroxyl, $-NHR_{10}$ or $-NR_{12}R_{13}$ where R_{10}, R_{12} and R_{13} are as defined in claim 1, R_5 is amino, arylalkyl, arylalkynyl, arylamino or halogen and R_6 is aryl, arylalkyl, arylalkenyl, arylalkynyl, or halogen.

17. A compound according to Claim 15 or 16 wherein R_4 is amino, methylamino, dimethylamino, carbamate, acylamino or heteroarylacylamino.

18. A compound according to any of Claims 15 to 17 wherein R_6 is chloro, iodo, phenyl, 2-phenylethyl or 2-phenylethynyl.

19. A pharmaceutical composition comprising a therapeutically effective amount of a compound according to any of Claims 1 to 18 in combination with a pharmaceutically acceptable carrier.

20. A method for inhibiting adenosine kinase comprising exposing adenosine kinase to an effective inhibiting amount of a compound according to any of Claims 1 to 18.

21. A method of treating cerebral ischemia, epilepsy, nociception, inflammation and sepsis in a subject in need of such treatment, comprising administering to the subject a therapeutically effective amount of a compound according to any of Claims 1 to 18.

INTERNATIONAL SEARCH REPORT

Inter nal Application No
PCT/US 96/09042

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D487/04 A61K31/505 C07F9/6561 A61K31/675
//(C07D487/04,239:00,209:00)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO,A,94 18215 (GENSIA) 18 August 1994 see page 5, line 7 - line 18; claim 1 ---	1,19,20
X	EP,A,0 496 617 (GENSIA) 29 July 1992 see page 3, line 13 - line 23; claim 1 ---	1,19,20
X	US,A,3 311 628 (PARTYKA) 28 March 1967 see column 1, paragraph 2; claim 1; example 17 ---	1,19,21
X	BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, vol. 3, no. 4, 1993, OXFORD, GB, pages 663-666, XP000600998 S. M. SIDDIQI ET AL.: "(+-)-7-Deazaaristeromycin lacking the hydroxymethyl substituent" see compound 5 and 9 and page 665, lines 4 and 5 --- -/--	1,19

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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"&" document member of the same patent family

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Date of the actual completion of the international search	Date of mailing of the international search report
9 September 1996	20.09.96

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Alfaro Faus, I

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Inter   onal Application No
PC /US 96/09042

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	NUCLEOSIDES & NUCLEOTIDES, vol. 12, no. 3-4, 1993, NEW YORK, US, pages 267-278, XP000600983 S. M. SIDDIQI ET AL.: "Enatiospecific synthesis of 5'-noraristeromycin and its 7-deaza derivative and a formal synthesis of (-)-5'-homoaristomycin" see compounds 3 and 10 and page 267 ---	1,19
X	JOURNAL OF MEDICINAL CHEMISTRY, vol. 10, no. 4, 1967, WASHINGTON US, pages 665-667, XP002012945 J. M. MONTGOMERY ET AL.: "Analogs of tubercidin" see compound 3c and table I ---	1,19
X	US,A,3 682 918 (J. DRUEY) 8 August 1972 see examples 14, lines 10,11 and 19,20 and example 19 -----	1,19

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FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Remark: Although claim 21 is directed to a method of treatment of (diagnostic method practised on) the human/animal body the search has been carried out and based on the alleged effects of the compound/composition.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/US 96/09042

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		US-A-	3600389	17-08-71